

Exhibit 3

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(54) Title: MONOCLONAL ANTIBODIES WITH REDUCED IMMUNOGENICITY			
(57) Abstract Antibodies having reduced immunogenicity and methods for making them are disclosed.			

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MONOCLONAL ANTIBODIES WITH REDUCED IMMUNOGENICITY

This application claims the benefit of U.S. Provisional Application No. 60/083,367, filed April 28, 1998.

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Field of the Invention

This invention relates to monoclonal antibodies (mAbs) having reduced immunogenicity in humans.

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Background of the Invention

Many potentially therapeutic mAbs are first generated in a murine hybridoma system for reasons of speed and simplicity. Non-human mAbs contain substantial stretches of amino acid sequences that will be immunogenic when injected 15 into a human patient. It is well known that after injection of a foreign antibody, such as a murine antibody, a patient can have a strong human anti-mouse antibody (HAMA) response that essentially eliminates the antibody's therapeutic utility after the initial treatment as well as the utility of 20 any other subsequently administered murine antibody.

Humanization techniques are well known for producing mAbs which exhibit reduced immunogenicity in humans while retaining the binding affinity of the original non-human parental mAb. See, e.g., those disclosed in U.S. Patent Nos. 25 5,585,089; 5,693,761; 5,693,762; and 5,225,539.

In general, these methods depend on replacing human variable heavy and light region complementarity determining regions (CDRs) with antigen specific non-human CDRs, a process known as CDR grafting. It is also well known that in 30 CDR grafting experiments the retention of the original antigen binding affinity is enhanced and in many cases depends on choosing human acceptor framework regions that most closely match the corresponding frameworks of the CDR donor antibody.

However, since the human genome contains a limited 35 repertoire of heavy and light chain framework regions, these methods suffer from the limitation of available human acceptor frameworks. This restriction in acceptor framework repertoire necessarily can limit the degree of match between 40 the non-human donor and the human acceptor antibody. Thus,

CDR grafting methods are limited by the known available repertoire of human VH and VL framework regions. Clearly, a need exists for an expanded range of acceptor V regions.

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Summary of the Invention

One aspect of the present invention is an antibody comprising donor CDRs derived from an antigen-specific donor antibody of a non-human species and acceptor framework residues derived from a non-human primate.

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Another aspect of the invention is a method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous non-human primate acceptor frameworks.

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Another aspect of the invention is a chimpanzee VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOS: 10, 11, 12, 13, 14, 15, 16, 17 or 18.

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Another aspect of the invention is a chimpanzee VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOS: 81, 82, 83, 84 or 85.

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Another aspect of the invention is a chimpanzee VK acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOS: 28, 29, 30, 31, 32, 33, 34, 35 or 36.

Another aspect of the invention is a chimpanzee VK acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOS: 86 or 87.

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Another aspect of the invention is a cynomolgus VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOS: 45, 46, 47, 48, 49, 50, 51 or 52.

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Another aspect of the invention is a cynomolgus VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOS: 88, 89, 90, 91, 92 or 93.

Another aspect of the invention is a cynomolgus VK acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOS: 59, 60, 61, 62, 63 or 64.

Another aspect of the invention is a cynomolgus VK acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOS: 94, 95 or 96.

Yet another aspect of the invention is an isolated
5 nucleic acid molecule encoding the amino acid sequence of SEQ ID NOS: 10, 11, 12, 13, 14, 15, 16, 17, 18, 28, 29, 30, 31, 32, 33, 34, 35 or 36.

Yet another aspect of the invention is an isolated
nucleic acid molecule encoding the amino acid sequence of SEQ
10 ID NOS: 81, 82, 83, 84, 85, 86 or 87.

Yet another aspect of the invention is an isolated
nucleic acid molecule encoding the amino acid sequence of SEQ
ID NOS: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or
64.

15 Yet another aspect of the invention is an isolated
nucleic acid molecule encoding the amino acid sequence of SEQ
ID NOS: 88, 89, 90, 91, 92, 93, 94, 95 or 96.

Brief Description of the Drawings

20 Figure 1 is an amino acid sequence of the engineered 4A6 VL region. Asterisks above the 4A6 sequence indicate the 4A6 framework residues retained in the engineered molecule. Bold and italicized letters indicate the CDRs.

25 Figure 2 is an amino acid sequence of the engineered 4A6 VH region. Asterisks above the 4A6 sequence indicate the 4A6 framework residues retained in the engineered molecule. Bold and italicized letters indicate the CDRs.

30 Figure 3 is an amino acid sequence alignment comparing the murine antibody B9VK with the closest matching chimpanzee VK and selected JK sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. The numbering convention is from Kabat et al., *infra*.

35 Figure 4 is an amino acid sequence alignment comparing the murine antibody B9VH with the closest matching chimpanzee VH and selected JH sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat et al., *infra*.

Figure 5 is an amino acid sequence alignment comparing the murine antibody 3G9V_K with the closest matching chimpanzee V_K and selected J_K sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat *et al.*, *infra*.

Figure 6 is an amino acid sequence alignment comparing the murine antibody 3G9VH with the closest matching chimpanzee V_H and selected J_H sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat *et al.*, *infra*.

Detailed Description of the Invention

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

The molecular genetic aspects of antibody structure have been reviewed by S. Tonegawa in *Nature* 302:575-581 (1983). Briefly, antibodies are heterodimers comprised of at least two heavy and two light chains. The N-terminal domain of each heavy and light chain, termed V_H and V_L, respectively, fold together to form the antigen combining site. On the genetic level, the V_L domain is encoded by two different gene segments, termed V_K or V_L, and J_K or J_L that join together to form one continuous V_L region. Similarly, the V_H domain is encoded by three gene segments, V_H, D_H, and J_H, that join together to form one continuous V_H region. Thus different V_L and V_H regions may be encoded by different combinations of V_K or V_L, J_K or J_L and V_H, D_H, and J_H. This combinatorial diversity is in part the means by which the immune response generates the myriad diversity of different antibody molecules and their associated antigen specificities.

On the protein level, each heavy and light V region domain may be further divided into three CDRs. Three heavy

and three light chain CDRs fold together to form the antigen binding surface and part of the underlying support structures that are required to maintain the exact three-dimensional structure of the antigen combining site. Flanking each CDR
5 are framework regions that in most cases do not directly interact with the specific antigen, but rather serve to form the scaffold which supports the antigen binding properties of the CDRs. Each heavy and light chain has four framework regions, three derived from the VH or VL gene segment, the
10 fourth is derived from the JH, JK, or J1 gene segment. Thus, the order of frameworks and CDRs from the N- terminus is framework I, CDRI, framework II, CDRII, framework III, CDRIII, framework IV. On the genetic level, all of framework I through Framework III is encoded by the V region gene
15 segment; CDRIII is encoded jointly by both the V region and J region gene segments; framework IV is encoded entirely from the J gene segment.

As used herein, "antibodies" refers to immunoglobulins and immunoglobulin fragments lacking all or part of an
20 immunoglobulin constant region, e.g., Fv, Fab, Fab' or F(ab')₂ and the like.

The term "donor antibody" refers to a monoclonal or recombinant antibody which contributes the nucleic acid sequences of its variable regions, CDRs or other functional
25 fragments or analogs thereof to an engineered antibody, so as to provide the engineered antibody coding region and resulting expressed engineered antibody with the antigenic specificity and neutralizing activity characteristic of the donor antibody.

30 The term "acceptor antibody" refers to monoclonal or recombinant antibodies heterologous to the donor antibody, which contributes all, or a portion, of the nucleic acid sequences encoding its heavy and/or light chain framework regions and/or its heavy and/or light chain constant regions
35 or V region subfamily consensus sequences to the engineered antibody.

A "functional fragment" is a partial heavy or light chain variable sequence (e.g., minor deletions at the amino or carboxy terminus of the immunoglobulin variable region)

which retains the same antigen binding specificity and affinity as the antibody from which the fragment was derived.

An "analog" is an amino acid sequence modified by at least one amino acid, wherein said modification can be 5 chemical or a substitution, which modification permits the amino acid sequence to retain the biological characteristics, e.g., antigen specificity and high affinity, of the unmodified sequence.

Methods are provided for making engineered antibodies 10 with reduced immunogenicity in humans and primates from non-human antibodies. CDRs from antigen-specific non-human antibodies, typically of rodent origin, are grafted onto homologous non-human primate acceptor frameworks.

Preferably, the non-human primate acceptor frameworks are 15 from Old World apes. Most preferably, the Old World ape acceptor framework is from *Pan troglodytes*, *Pan paniscus* or *Gorilla gorilla*. Particularly preferred is the chimpanzee *Pan troglodytes*. Also preferred are Old World monkey acceptor frameworks. Most preferably, the Old World monkey 20 acceptor frameworks are from the genus *Macaca*. Particularly preferred is the cynomolgus monkey *Macaca cynomolgus*.

Particularly preferred chimpanzee (*Pan troglodytes*) heavy chain variable region frameworks (VH) are CPVH41-12 having the framework I, II and III amino acid sequence shown 25 in SEQ ID NO: 10 and the framework IV amino acid sequence shown in SEQ ID NO: 83; CPVH41-1 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 11 and the framework IV amino acid sequence shown in SEQ ID NO: 85; CPVH41-4 having the framework I, II and III amino acid 30 sequence shown in SEQ ID NO: 12; CPVH41-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 13; CPVH41-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 14, CPVH41-9 having the framework I, II and III amino acid sequence shown in SEQ ID 35 NO: 15 and the framework IV amino acid sequence shown in SEQ ID NO: 81; CPVH41-10 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 16 and the framework IV amino acid sequence shown in SEQ ID NO: 82; CPVH41-18 having the framework I, II and III amino acid sequence shown in SEQ 40 ID NO: 17; and CPVH41-19 having the framework I, II and III

amino acid sequence shown in SEQ ID NO: 18 and the framework IV amino acid sequence shown in SEQ ID NO: 84.

Particularly preferred chimpanzee (*Pan troglodytes*) light chain kappa variable region frameworks (VK) are CPVK46-1 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 28; CPVK46-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 29; CPVK46-4 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 30; CPVK46-5 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 31; CPVK46-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 32 and the framework IV amino acid sequence shown in SEQ ID NO: 86; CPVK46-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 33 and the framework IV amino acid sequence shown in SEQ ID NO: 87; CPVK46-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 34; CPVK46-11 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 35; and CPVK46-14 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 36.

Particularly preferred cynomolgus (*Macaca cynomolgus*) heavy chain variable region frameworks (VH) are CYVH2-1 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 45 and the framework IV amino acid sequence shown in SEQ ID NO: 88; CYVH2-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 46 and the framework IV amino acid sequence shown in SEQ ID NO: 89; CYVH2-4 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 47 and the framework IV amino acid sequence shown in SEQ ID NO: 90; CYVH2-5 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 48 and the framework IV amino acid sequence shown in SEQ ID NO: 93; CYVH2-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 49 and the framework IV amino acid sequence shown in SEQ ID NO: 91; CYVH2-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 50; CYVH2-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 51; and CYVH2-10 having the

framework I, II and III amino acid sequence shown in SEQ ID NO: 52 and the framework IV amino acid sequence shown in SEQ ID NO: 92.

Particularly preferred cynomolgus (*Macaca cynomolgus*)
5 light chain kappa variable region frameworks (V_k) are CYV_k4-2 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 59; CYV_k4-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 60 and the framework IV amino acid sequence shown in SEQ ID NO: 94; CYV_k4-5 having
10 the framework I, II and III amino acid sequence shown in SEQ ID NO: 61; CYV_k4-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 62 and the framework IV amino acid sequence shown in SEQ ID NO: 95; CYV_k4-10 having the framework I, II and III amino acid sequence shown in SEQ
15 ID NO: 63; and CYV_k4-11 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 64 and the framework IV amino acid sequence shown in SEQ ID NO: 96.

Isolated nucleic acid molecules encoding the chimpanzee VH and V_k acceptor framework I, II and III amino acid sequences of SEQ ID NOS: 10, 11, 12, 13, 14, 15, 16, 17, 18, 20 28, 29, 30, 31, 32, 33, 34, 35 or 36 and the framework IV amino acid sequences of SEQ ID NOS: 81, 82, 83, 84 ,85, 86 or 87 are also part of the present invention. Further, isolated nucleic acid molecules encoding the cynomolgus VH and V_k
25 acceptor framework I, II and III amino acid sequences of SEQ ID NOS: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or 64 and the framework IV amino acid sequences of SEQ ID NOS: 88, 89, 90, 91, 92, 93, 94, 95 or 96 are also part of the present invention. Nucleic acid sequences encoding
30 functional fragments or analogs of the VH and V_k acceptor framework amino acid sequences are also part of the present invention.

In addition to isolated nucleic acid sequences encoding VH and V_k acceptor frameworks described herein, nucleic acid sequences complementary to these framework regions are also encompassed by the present invention. Useful DNA sequences include those sequences which hybridize under stringent hybridization conditions to the DNA sequences. See, T.
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Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory (1982), pp. 387-389. An example of one such stringent hybridization condition is hybridization at 4XSSC at 65°C, followed by a washing in 5 0.1XSSC at 65°C for one hour. Alternatively, an exemplary stringent hybridization condition is 50% formamide, 4XSSC at 42°C. Preferably, these hybridizing DNA sequences are at least about 18 nucleotides in length.

Suitable frameworks are selected by computer homology 10 searching among members of a database of Old World ape or monkey VH and VL regions. The framework portions of primate antibodies are useful as components of therapeutic antibodies. Moreover, primate antibody frameworks will be tolerated when used in the treatment of humans due to the 15 close sequence homology between the genes of the primates and humans. Thus, the present invention provides for the grafting of CDRs from an antigen specific non-human donor antibody to acceptor V regions derived from non-human primate species.

The antigen specificity and binding kinetics of the 20 donor antibody, which may be of rodent or any other non-human origin, are best preserved by selecting primate acceptor V regions that are determined by computer homology searching to be most similar to the donor antibody. Alternatively, the 25 acceptor antibody may be a consensus sequence generated from primate V region subfamilies, or portions thereof, displaying the highest homology to the donor antibody.

The resulting engineered constructs, in which the donor 30 CDRs are grafted onto primate acceptor frameworks, are subsequently refined by analysis of three-dimensional models based on known antibody crystal structures as found, e.g., in the Protein Data Bank, <http://www.pdb.bnl.gov/pdb-bin/pdbmain>. Alternatively, computer generated three-dimensional models of the donor antibody may be computed by 35 means of commercially available software such as "AbM" (Oxford Molecular, Oxford, UK).

Structural analysis of these models may reveal donor framework residues that are CDR-contacting residues and that are seen to be important in the presentation of CDR loops,

and therefore binding avidity. A CDR-contacting residue is one which is seen in three-dimensional models to come within the van der Waals radius of a CDR residue, or could interact with a CDR residue via a salt bridge or by hydrophobic interaction. Such donor framework (CDR-contacting) residues may be retained in the engineered construct.

The modeling experiments can also reveal which framework residues are largely exposed to the solvent environment. The engineered constructs may be further improved by substituting some or all of these solvent-accessible amino acid residues with those found at the same position among human V regions most homologous to the engineered construct as disclosed in U.S. Patent No. 5,639,641.

The engineered V regions are then joined to one or more different human or Old World ape constant regions depending on the desired secondary immune functions such as complement fixation or Fc receptor binding. Human constant regions can be selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. An IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function can also be selected. See U.S. Patent Nos. 5,624,821 and 5,648,260.

The complete heavy and light chain genes are transferred to suitable expression vectors and co-expressed in the appropriate host cells such as Chinese hamster ovary, COS or myeloma cells. The resulting engineered antibody is expected to be of substantially reduced immunogenicity when administered to humans, and to retain full binding affinity for antigen.

Acceptor V regions can be isolated specifically for each donor V region by directed PCR methodology where a non-human primate cDNA library is surveyed for acceptor frameworks most similar to the donor antibody. Oligonucleotide PCR primers homologous to the donor antibody framework I (paired with C-region 3' PCR primers) are used to direct PCR amplification of a non-human primate, e.g., chimpanzee lymphocyte cDNA library. This would select for V-regions with framework I regions similar to the donor antibody, and sequence analysis of the obtained clones would reveal the associated framework

II and III (and IV) sequences. 3' PCR primers would then be designed based on the knowledge of the non-human primate framework III sequences thus obtained, and used to direct PCR amplification of the original cDNA library together with a 5 vector-specific 5' PCR primer. cDNA clones obtained from the second round of PCR amplification would have framework I and III sequences most similar to the donor antibody, and the framework II sequences would display a similar degree of sequence homology.

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The present invention will now be described with reference to the following specific, non-limiting examples.

Example 1

15 Random cDNA Cloning and Sequence Analysis of Chimpanzee VH Regions

Five ml of peripheral blood was collected and pooled from three chimpanzees (*Pan troglodytes*) and peripheral blood mononuclear cells were isolated by standard density 20 centrifugation methods. These cells, which include antibody producing lymphocytes, were dissolved in TRIzol reagent (GIBCO, Gaithersburg, MD, USA) and total RNA was recovered from this material by solvent extraction and precipitation according to the manufacturer's specifications.

25 Chimpanzee heavy chain V regions were cloned from the total RNA using Marathon RACE methodology (Clontech, Palo Alto, CA, USA) following exactly the manufacturer's protocol using 3' Cg1 gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised 30 from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct heavy chain V region clones, nine were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the chimpanzee 35 VH cDNA clones 41-12, 41-1, 41-4, 41-7, 41-8, 41-9, 41-10, 41-18 and 41-19 are shown in SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8 and 9, respectively. The amino acid sequences of the region from the first amino acid of the mature VH region to the second conserved cysteine residue at position 92, 40 adjacent to CDR III of these clones, namely, CPVH41-12,

CPVH41-1, CPVH41-4, CPVH41-7, CPVH41-8, CPVH41-9, CPVH41-10, CPVH41-13 and CPVH41-19 are shown in SEQ ID NOS: 10, 11, 12, 13, 14, 15, 16, 17 and 18, respectively. The amino acid sequence of the region encoding framework IV of these clones 5 for CPVH41-9, CPVH41-10, CPVH41-12, CPVH41-19 and CPVH 41-1 are shown in SEQ ID NOS: 81, 82, 83, 84 and 85, respectively.

The chimpanzee VH amino acid sequences from the mature N-terminus and the second conserved cysteine residue at position 92, adjacent to CDRIII, were used as query sequences 10 in computer homology searching of the Kabat database of Sequences of Proteins of Immunological Interest (<ftp://ncbi.nlm.nih.gov/repository/kabat/>) The results of this analysis are shown in Table 1.

In each case, the closest match was with a human VH 15 region, displaying between 76% (41-1/HHC20G) and 94% (41-10/HHC20Y) sequence identity at the amino acid level. Matches were found for each of the three major human VH 20 subgroups, indicating that the chimpanzee VH repertoire includes at least some members homologous to each of the major human subgroups. The human subgroup homology is presented in Table 1.

Clone	Closest Match	Overall Amino Acid Homology	Table 1	
			VH	Subgroup Match
41-4	HHC10X	88%		I
41-9	HHC10Y	92		I
41-18	HHC10D	84		I
41-1	HHC20G	76		II
41-10	HHC20Y	94		II
41-12	HHC20C	83		II
41-7	HHC30T	80		III
41-8	HHC30T	79		III
41-19	HHC30S	82		III

The results show that the overall sequence identity between the chimpanzee and human VH regions ranged between 76 and 95% with a mean identity of 84%. Based on this 40 observation, further sampling of the chimpanzee random VH library will likely provide a substantially greater diversity of VH sequences from which to choose optimum acceptor frameworks for each particular donor VH region.

Example 2Random cDNA Cloning and Sequence Analysis of Chimpanzee VK Regions

Chimpanzee light chain VK regions were cloned from the total RNA using Marathon RACE methodology (Clontech, Palo Alto, CA, USA) following exactly the manufacturer's protocol and CK 3' gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct light chain VK region clones, nine were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the chimpanzee VK cDNA clones 46-1, 46-3, 46-4, 46-5, 46-6, 46-7, 46-8, 46-11 and 46-14 are shown in SEQ ID NOS: 19, 20, 21, 22, 23, 24, 25, 26 and 27, respectively. The amino acid sequences of the region from the first amino acid of the mature VK region to the second conserved cysteine residue at position 88, adjacent to CDR III of these clones, namely CPVK46-1, CPVK46-3, CPVK46-4, CPVK46-5, CPVK46-6, CPVK46-7, CPVK46-8, CPVK46-11 and CPVK46-14 are shown in SEQ ID NOS: 28, 29, 30, 31, 32, 33, 34, 35 and 36, respectively. The amino acid sequences of the region encoding framework IV of these clones for CPVK46-6 and CPVK46-7 are shown in SEQ ID NOS: 86 and 87, respectively.

The chimpanzee VK amino acid sequences comprising the mature N-terminus and the second conserved cysteine residue at position 88 were used as query sequences in computer homology searching of the Kabat database. The results of this analysis are shown in Table 2. In each case the closest match was with a human VK region, displaying between 68% (46-4/HKL310) and 97% (46-11/HKL106) sequence identity at the amino acid level. It is evident that the chimpanzee VK sequences are distinct from the collection of human VK found in the Kabat database.

The human subgroup homology is presented in Table 2. Of the four major human VK subgroups, matches were found for the two most frequently isolated, indicating that the chimpanzee VK repertoire is at least homologous to members of the majority of the human VK repertoire. Further sampling of the chimpanzee VK cDNA library will likely identify a greater diversity of chimpanzee VK regions, including ones homologous to the remaining two human VK subgroups (VKII and VKIV).

			Table 2	
			Overall Amino Acid Homology	
	Clone	Closest Match		VH Subgroup Match
10	46-1	HKL10C	85%	I
	46-3	HKL 100	91	I
	46-5	HKL 100	91	I
15	46-7	HKL 100	81	I
	46-8	HKL 10N	90	I
	46-11	HKL 106	97	I
	46-14	HKL 100	92	I
	46-4	HKL 310	68	III
20	46-6	HKL 310	96	III

Example 3

Random cDNA Cloning and Sequence Analysis of Cynomolgus VH Regions

25 Splenic RNA was recovered from a single donor cynomolgus monkey (*Macaca cynomolgus*) by means of standard laboratory practice. Cynomolgus heavy chain V regions were cloned from the total RNA using Marathon RACE methodology (Clontech, Palo Alto, CA, USA) following exactly the manufacturer's protocol
 30 using 3' Cg1 gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct heavy V region clones, eight were selected randomly
 35 for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the Cynomolgus VH cDNA clones 2-1, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8 and 2-10 are shown in SEQ ID NOS: 37, 38, 39, 40, 41, 42, 43 and 44, respectively. The amino acid sequences of the region from the first amino acid
 40 of the mature VH region to the second conserved cysteine residue at position 92, adjacent to CDR III of these clones, namely CyVH2-1, CyVH2-3, CyVH2-4, CyVH2-5, CyVH2-6, CyVH2-7, CyVH2-8 and CyVH2-10 are shown in SEQ ID NOS: 45, 46, 47, 48,

49, 50, 51 and 52, respectively. The amino acid sequences of the region encoding framework IV of these clones for CyVH2-1, CyVH2-3, CyVH2-4, CyVH2-6, CyVH2-10 and CyVH2-5 are shown in SEQ ID NOS: 88, 89, 90, 91, 92 and 93, respectively.

5 The cynomolgus VH amino acid sequences from the mature N-terminus and the second conserved cysteine residue at position 92, adjacent to CDRIII, were used as query sequences in computer homology searching of the Kabat database. The results of this analysis are shown in Table 3. In each case
10 the closest match was with a human VH region, displaying between 62% (2-6/ HHC20E) and 84% (2-5/ HHC20F) sequence identity at the amino acid level. It is evident that the cynomolgus VH sequences are distinct from the collection of human VH found in the Kabat database. Matches were found for
15 each of the three major human VH subgroups, indicating that the cynomolgus VH repertoire includes at least some members homologous to each of the major human subgroups. The human subgroup homology is presented in Table 3.

20

Clone	Closest Match	Overall Amino Acid Homology	Table 3	
			VH Subgroup	Match
2-4	HHC10Y	83%	I	
2-10	HHC20G	83	II	
25 2-8	HHC20F	74	II	
2-6	HHC20E	62	II	
2-5	HHC20F	84	II	
2-3	HHC20F	75	II	
2-1	HHC316	71	III	
30 2-7	HHC31C	81	III	

25 The results show that the overall sequence identity between the cynomolgus and human VH regions ranged between 62 and 84% with a mean identity of 77%. Based on this observation, further sampling of the cynomolgus random VH library will likely provide a substantially greater diversity of VH sequences from which to choose optimum acceptor frameworks for each particular donor VH region.

40

Example 4

Random cDNA Cloning and Sequence Analysis of Cynomolgus VK Regions

Cynomolgus light chain VK regions were cloned from the total splenic RNA using Marathon RACE methodology (Clontech,

Palo Alto, CA, USA) following exactly the manufacturer's protocol and CK 3' gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a 5 plasmid vector. Although this cDNA library contains many distinct light chain VK region clones, six were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the Cynomolgus 10 VK cDNA clones 4-2, 4-3, 4-5, 4-6, 4-10 and 4-11 are shown in SEQ ID NOS: 53, 54, 55, 56, 57 and 58, respectively. The amino acid sequences of the region from the first amino acid 15 of the mature VK region to the second conserved cysteine residue at position 88, adjacent to CDRIII, of these clones, namely CyVK4-2, CyVK4-3, CyVK4-5, CyVK4-6, CyVK4-10 and CyVK4- 20 11 are shown in SEQ ID NOS: 59, 60, 61, 62, 63 and 64, respectively. The amino acid sequences encoding the framework IV region of these clones for CyVK4-3, CyVK4-6 and CyVK4-11 are shown in SEQ ID NOS: 94, 95 and 96, respectively.

The cynomolgus VK amino acid sequences comprising the mature N-terminus and the second conserved cysteine residue at position 88 were used as query sequences in computer homology searching of the Kabat database. The results of this analysis are shown in Table 4. In each case the closest 25 match was with a human VK region, displaying between 73% (4-11/ HKL10S) and 94% (4-3/ HKL400) sequence identity at the amino acid level. It is evident that the cynomolgus VK sequences are distinct from the collection of human VK found in the public genetic databases. The human subgroup homology 30 is presented in Table 4. Matches were found for three of the four major human VK subgroups, indicating that the cynomolgus VK repertoire is largely homologous to members of the majority of the human VK repertoire. Further sampling of the cynomolgus VK cDNA library will likely identify a greater 35 diversity of cynomolgus VK regions, including ones homologous to the remaining human VK subgroup (VKIII).

Table 4
Overall Amino Acid Homology

Clone	Closest Match	Overall Amino Acid Homology	VK Subgroup Match
5 4-6	HKL10L	80%	I
4-2	HKL10Z	83	I
4-11	HKL10S	73	I
4-10	HKL10F	93	I
4-5	HKL209	86	II
10 4-3	HKL400	94	IV

The results show that the overall sequence identity between the cynomolgus and human VK regions ranged between 73 and 94% with a mean identity of 85%. Based on this observation, further sampling of the cynomolgus random VK library will provide a substantially greater diversity of VK sequences from which to choose optimum acceptor frameworks for each particular donor VK region.

20 **Example 5**

Preparation of Engineered Anti-IL-5 Monoclonal Antibodies

The VK and VH genes of the rat anti-interleukin-5 (IL-5) antibody 4A6 are shown in SEQ ID NOS: 65 and 66, respectively. These genes encode a high affinity neutralizing monoclonal antibody specific for human IL-5 useful for the treatment of asthma. See U.S. Patent No. 5,693,323.

The 4A6 light chain was engineered as follows. The sequence of donor antibody Vk4A6 (SEQ ID NO: 65) was aligned with the acceptor antibody light chain VK region from the chimpanzee Mab C108G (*Mol. Immunol.* 32:1081-1092 (1995)) (SEQ ID NO: 67) as shown in Fig. 1. Since native Vk4A6 has a unique deletion of residue 10, the sequence alignment included the insertion of a gap at that position. The CDR residues were identified as defined by the convention of Kabat *et al.* in *Sequences of Proteins of Immunological Interest*, 4th ed., U.S. Department of Health and Human Services, National Institutes of Health (1987).

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this

CDR-contacting set were compared among the aligned VK4A6 and VHC108G sequences, and the positions of the set that differed between the VK4A6 and the VHC108G were marked (Fig. 1, asterisks). The CDRs and the marked framework residues of 5 VK4A6 (the donor antibody) were transferred replacing the corresponding residues of VHC108G (the acceptor antibody). The completed engineered 4A6 light chain V region is shown in SEQ ID NO: 68. Six donor framework residues were retained in the engineered molecule at residues 1 to 4, 49 and 60.

10 In analogous fashion, a similar method was used to engineer the 4A6 heavy chain. The sequence of donor antibody VH4A6 (SEQ ID NO: 66) was aligned with the acceptor antibody heavy chain V region from the chimpanzee Mab C108G (SEQ ID NO: 69) as shown in Fig. 2. A large gap was introduced in 15 the VH4A6 CDRIII alignment, as CDRIII of VHC108G is 10 residues longer. CDR residues were identified as defined by the convention of Kabat et al., *supra*.

Framework residues that could influence CDR presentation 20 were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VH4A6 and VHC108G sequences, and the positions of the set that differed between the VH4A6 and the VHC108G were marked (Fig. 2, asterisks). In total, 11 such CDR contacting residues that 25 differed between VH4A6 and the VHC108G were selected and marked. The CDRs and the marked CDR contacting framework residues of VH4A6 (the donor antibody) were transferred replacing the corresponding residues of VHC108G (the acceptor antibody). The completed engineered 4A6 heavy chain V region 30 is shown in SEQ ID NO: 70. Eleven donor framework residues were retained in the engineered molecule at residues 27, 30, 38, 49, 66, 67, 69, 71, 73, 78 and 94.

The engineered 4A6 can be expressed in cells using 35 methods well known to those skilled in the art. Briefly, genes encoding the complete engineered 4A6 VH and VK regions can be assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing the desired antibody constant regions. Such an expression vector will contain selectable markers, for

example, neomycin resistance and regulatory sequences, for example, the CMV promoter, required to direct the expression of full-length antibody heavy and light chains. Subsequently, transfection of the appropriate host cell, for example, chinese hamster ovary, would result in the expression of fully active engineered 4A6.

Example 6

Preparation of Engineered Anti-Integrin Monoclonal Antibodies

10 The VK and VH genes of the murine anti-integrin antibody B9 are shown in SEQ ID NOS: 71 and 72, respectively. These genes encode a high affinity neutralizing monoclonal antibody specific for human integrin $\alpha v \beta 3$ useful for the treatment of vascular diseases.

15 The B9 light chain was engineered as follows. The amino acid sequence of donor antibody VKB9 (SEQ ID NO: 72) was compared to each of the nine chimpanzee VK sequences described above and percent sequence identity determined by computer homology searching using the LASERGENE program "MEGALIGN" (DNASTAR, Inc., Madison, WI). Clones CPVK46-3 (SEQ ID NO: 29) and CPVK46-14 (SEQ ID NO: 36) were identified as the chimpanzee VK regions with the highest overall sequence similarity (77%) to the B9 donor VK. CPVK46-3 was selected as the acceptor framework.

25 Similarly, the chimpanzee JK gene segment of CPVK46-1 (SEQ ID NO: 97) was selected as acceptor framework IV. The sequences of the donor VKB9 and acceptor CPVK46-3, CPVK46-1 V regions were aligned and the positions of their respective framework and CDRs were determined as shown in Fig. 3.

30 The CDR residues were identified as defined by the convention of Kabat et al., *supra*. The results show that VKB9 and CPVK46-3 share 77% overall sequence identity, with the framework regions I through III sharing 81% sequence identity.

35 Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this

CDR-contacting set were compared among the aligned VkB9 and CPV_k46-3 sequences, and none of this set were found that differed between the VkB9 and the CPV_k46-3. Accordingly, only the CDRs of VkB9 (the donor antibody) were transferred
5 replacing the corresponding residues of CPV_k46-3 (the acceptor antibody). Lastly, the framework IV sequences of CPV_k46-1 replaced the corresponding framework IV residues of the B9 light chain variable region. The completed engineered
10 B9 light chain V region is shown in SEQ ID NO: 73. No donor framework residues were retained in the engineered light chain variable region.

The B9 heavy chain was engineered in analogous fashion. The amino acid sequence of donor antibody VHB9 (SEQ ID NO: 71) was compared to each of the nine chimpanzee VH sequences
15 described above by computer homology searching. Clone CPVH41-18 (SEQ ID NO: 17) was identified as the chimpanzee VH region with the highest overall sequence similarity (58%) to the B9 donor VH.

The chimpanzee JH gene segment of CPVH41-10 (SEQ ID NO:
20 82) was selected as acceptor framework IV. The sequences of the donor VHB9 and chimpanzee acceptor V regions were aligned and the positions of their respective framework and CDRs determined as shown in Fig. 4.

The CDR residues were identified as defined by the
25 convention of Kabat et al., *supra*. The results show that VHB9 and CPVH41-18 share 58% overall sequence identity, with the framework regions I through III sharing 65% sequence identity.

Framework residues that could influence CDR presentation
30 were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VHB9 and CPVH41-18 sequences, and the nine residues of the set that differed between VHB9 and the chimpanzee acceptor frameworks
35 were marked. The CDRs and the marked framework residues of donor antibody VHB9 were transferred replacing the corresponding residues of CPVH41-18 (the acceptor antibody). Lastly, the framework IV sequences of CPVH41-10 replaced the corresponding framework IV residues of the B9 heavy chain
40 variable region. The completed engineered B9 heavy chain V

region is shown in SEQ ID NO: 74. Nine donor framework residues were retained in the engineered heavy chain variable region at positions 24, 27, 38, 48, 66, 67, 69, 93 and 94.

5

Example 7

Expression and Characterization of Engineered Anti-Integrin Monoclonal Antibodies

The engineered B9 antibody was expressed in cells using methods well known to those skilled in the art. Briefly, 10 genes encoding the complete engineered B9 VH and VK regions were assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing IgG1,κ antibody constant regions. The expression vector contained a selectable marker for neomycin resistance 15 and CMV promoter regulatory sequences. Subsequent transfection of a COS host cell resulted in the expression of engineered B9 (CPB9).

The relative binding avidity of CPB9 was compared to that of the original murine B9 antibody as follows. CPB9 20 antibodies present in culture supernatants from cells maintained in culture for 5 days after transfection with the expression constructs were compared to the parental murine B9 antibody using the ORIGEN technology (IGEN Inc, Gaithersburg, MD). Briefly, different dilutions of the B9 variants were 25 incubated with purified human $\alpha v\beta 3$ integrin which had previously been biotinylated, and an electrochemiluminescent TAG moiety specific for the antibody C regions. B9 variant antibody bound to the integrin was measured by capturing the immune complexes onto streptavidin beads followed by analysis 30 on the ORIGEN instrument. The results showed that the CPB9 and the murine B9 binding curves were displaced only by about 3-fold indicating that the overall specific binding avidity of CPB9 and murine B9 for $\alpha v\beta 3$ are within three-fold of each other. Accordingly, the results show that the CDR grafting 35 of rodent CDRs onto chimpanzee frameworks as described in the present invention retained nearly all of the binding avidity of the parent rodent mAb.

Example 8Preparation of Engineered Anti-Erythropoietin Receptor
Monoclonal Antibodies

The VH and VK genes of the murine anti-erythropoietin receptor antibody 3G9 are shown in SEQ ID NOS: 75 and 76, respectively. These genes encode a high affinity neutralizing monoclonal antibody specific for human erythropoietin receptor (EPOr) useful for the treatment of hematopoietic disorders.

The 3G9 light chain was engineered as follows. The amino acid sequence of donor antibody VK3G9 (SEQ ID NO: 76) was compared to each of the nine chimpanzee VK sequences described above by computer homology searching as described above. Clones CPVK46-3 (SEQ ID NO: 29), CPVK46-5 (SEQ ID NO: 31), CPVK46-8 (SEQ ID NO: 34) and CPVK46-14 (SEQ ID NO: 36) were identified as the chimpanzee VK regions with the highest overall sequence similarity (65%) to the 3G9 donor VK. CPVK46-14 was selected as the acceptor framework.

The chimpanzee JK gene segment of CPVK46-14 was identical to that of CPVK46-1 (SEQ ID NO: 97) and was selected as acceptor framework IV. The sequences of the donor VK3G9 and acceptor CPVK46-14 V regions were aligned and the positions of their respective framework and CDRs were determined as shown in Fig. 5.

The CDR residues were identified as defined by the convention of Kabat et al., *supra*. The results show that VK3G9 and CPVK46-14 share 65% overall sequence identity, with the framework regions I through III sharing 73% sequence identity.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VK3G9 and CPVK46-14 sequences, and the positions of this set that differed between VK3G9 and the CPVK46-3 were marked. The CDRs and marked residues of VK3G9 (the donor antibody) were

transferred replacing the corresponding residues of CPVK46-14 (the acceptor antibody). Lastly, the framework IV sequences of CPVK46-14 replaced the corresponding framework IV residues of the 3G9 light chain variable region. The completed 5 engineered 3G9 light chain V region is shown in SEQ ID NO: 77. Three donor framework residues were retained in the engineered light chain variable region at positions 3, 46 and 60.

The 3G9 heavy chain was engineered in analogous fashion. 10 The amino acid sequence of donor antibody VH3G9 (SEQ ID NO: 75) was compared to each of the 9 chimpanzee VH sequences described above by computer homology searching. Clone CPVH41-18 (SEQ ID NO: 17) was identified as the chimpanzee VH region with the highest overall sequence similarity (53%) to 15 the 3G9 donor VH.

The chimpanzee JH gene segment of CPVH41-18 was identical to CPVH41-9 (SEQ ID NO: 81) and was selected as acceptor framework IV. The sequences of the donor VH3G9 and chimpanzee acceptor V regions were aligned and the positions 20 of their respective framework and CDRs determined as shown in Fig. 6.

The CDR residues were identified as defined by the convention of Kabat *et al.*, *supra*. The results show that VH3G9 and CPVH41-18 share 53% overall sequence identity, with 25 the framework regions I through III sharing 62% sequence identity.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this 30 CDR-contacting set were compared among the aligned VH3G9 and CPVH41-18 sequences, and the twelve residues of the set that differed between VH3G9 and the chimpanzee acceptor frameworks were marked. The CDRs and the marked framework residues of donor antibody VH3G9 were transferred replacing the 35 corresponding residues of CPVH41-18 (the acceptor antibody). Lastly, the framework IV sequences of CPVH41-18 replaced the corresponding framework IV residues of the 3G9 heavy chain variable region. The completed engineered 3G9 heavy chain V region is shown in SEQ ID NO: 78. Twelve donor framework 40 residues were retained in the engineered heavy chain variable

region at positions 24, 27, 30, 38, 48, 66-69, 71, 73, and 94.

Example 9

5 **Expression and Characterization of Engineered anti-Erythropoietin Receptor Monoclonal Antibodies**

The engineered 3G9 antibody was expressed in cells using methods well known to those skilled in the art. Briefly, genes encoding the complete engineered 3G9 VH and VK regions 10 were assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing IgG1,κ antibody constant regions. The expression vector contained a selectable marker for neomycin resistance and CMV promoter regulatory sequences. Subsequent 15 transfection of COS host cells resulted in the expression of engineered 3G9 (CP3G9).

Culture supernatants from COS cells transiently transfected with chimpanzee framework engineered 3G9 were compared with another 3G9 variant for the ability to bind 20 human EPOR. The entire extracellular domain of the EPOR was expressed as recombinant protein, purified, and adsorbed onto the wells of ELISA plates. Dilutions of different antibodies were then tested for the ability to specifically bind to the solid phase associated EPOR.

25 HZ3G9 is a humanized variant of 3G9 in which human frameworks were used in traditional CDR grafting experiments. The humanized 3G9 heavy chain amino acid sequence is shown in SEQ ID NO: 79. The humanized 3G9 light chain sequence is shown in SEQ ID NO: 80. Previous experiments showed that 30 HZ3G9 retained the full binding affinity and avidity of the parental murine 3G9. Accordingly, since HZ3G9G1 is identical to the chimpanzee version in all respects except the V region cassette, it was used in the present comparative binding experiments as a surrogate for murine 3G9. Negative control 35 antibodies were also tested, including HZD12 which is a humanized antibody specific for human integrin, and CPB9 which is a chimpanzee framework engineered antibody specific for human integrins described above. Different concentrations of the 3G9 variants and control antibodies 40 were incubated for one hour. After washing, the bound

antibodies were detected by incubation with anti-human H+L antibody-enzyme conjugate, a final wash, and addition of chromagen.

The binding curves obtained for CP3G9 and HZ3G9 were superimposable. This result indicates that the human and the chimpanzee framework engineered versions of 3G9 have identical overall binding avidity for the specific antigen human EPOr. Since the constant regions of HZ3G9 and CP3G9 are identical, the results also suggest the full binding affinity of the original rodent 3G9 is retained in the chimpanzee version of 3G9. Accordingly, the results show that CDR grafting of rodent CDRs onto chimpanzee acceptor frameworks as described in the present invention retained the full binding avidity of the parental rodent antibody.

A BIAcore analysis (Pharmacia) was performed to determine the binding affinity for human EPOr of murine 3G9 and CP3G9. The interaction of CP3G9 as well as murine 3G9 with EPOr was characterized using a BIAcore 1000 biosensor. Descriptions of the instrumentation and the sensor surfaces are described in Brigham-Burke et al., *Anal. Biochem.*, 205:125-131 (1992).

CP3G9 was captured onto a sensor surface of immobilized protein A. The kinetic binding constants were determined by passing solutions of monomeric EPOr over the surface and monitoring binding versus time. The equilibrium dissociation constant for the interaction was then derived from the ratio of the kinetic constants. The parent murine 3G9 was captured onto a surface of protein A captured rabbit anti-mouse Fc specific polyclonal antibody. The kinetics and dissociation constant for the interaction with EPOr was determined as described above. All measurements were made in 10 mM sodium phosphate, 150 mM NaCl pH 7.2 3 mM EDTA and 0.005% Tween 20. The flow rate was 60 uL/min. The temperature was 20° C.

	k_{ass} ($M^{-1}s^{-1}$)	k_{diss} (s^{-1})	K_D (nM)
murine 3G9	1.2×10^6	4.0×10^{-3}	3.3
CP3G9	1.0×10^6	9.1×10^{-3}	9.1

35

These results show that the dissociation equilibrium constants determined for the murine and chimpanzee framework versions of 3G9 are within three fold of each other. This

data is in good agreement with the results of the ELISA-based study described above. Accordingly, the results show that the process used in generating the chimpanzee version of 3G9 largely retained the binding affinity of the original rodent
5 mAb.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof, and, accordingly, reference should be
10 made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

Claims

1. An antibody comprising donor CDRs derived from an antigen-specific donor antibody of a non-human species and acceptor framework residues derived from a non-human primate.
2. The antibody of claim 1 wherein the non-human primate is an Old World ape.
3. The antibody of claim 2 wherein the Old World ape is *Pan troglodytes*, *Pan paniscus* or *Gorilla gorilla*.
4. The antibody of claim 3 wherein the Old World ape is *Pan troglodytes*.
5. The antibody of claim 1 further comprising one or more CDR-contacting residues of the donor antibody.
6. The antibody of claim 1 comprising human or Old World ape constant regions.
7. The antibody of claim 1 wherein one or more solvent-exposed framework residues are replaced with corresponding residues from a homologous selected non-human primate framework.
8. The antibody of claim 1 wherein the non-human primate is an Old World monkey.
9. The antibody of claim 8 wherein the Old World monkey genus is *Macaca*.
10. The antibody of claim 9 wherein the Old World monkey is *Macaca cynomolgus*.
11. The antibody of claim 8 further comprising one or more CDR-contacting residues of the donor antibody.
12. The antibody of claim 8 comprising human or Old World ape constant regions.

13. The antibody of claim 8 wherein one or more solvent-exposed framework residues are replaced with corresponding residues from a homologous selected non-human primate framework.

14. A method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous Old World ape acceptor frameworks.

15. The method of claim 14 wherein the Old World ape acceptor framework is from *Pan troglodytes*, *Pan paniscus* or *Gorilla gorilla*.

16. The method of claim 15 wherein the Old World ape acceptor framework is from *Pan troglodytes*.

17. A method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous Old World monkey acceptor frameworks.

18. The method of claim 17 wherein the Old World monkey acceptor framework is from the genus *Macaca*.

19. The method of claim 18 wherein the Old World Monkey acceptor framework is from *Macaca cynomolgus*.

20. A chimpanzee VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOS: 10, 11, 12, 13, 14, 15, 16, 17 or 18.

21. A chimpanzee VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOS: 81, 82, 83, 84 or 85.

22. A chimpanzee VK acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOS: 28, 29, 30, 31, 32, 33, 34, 35 or 36.

23. A chimpanzee V_K acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOS: 86 or 87.

24. A cynomolgus VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOS: 45, 46, 47, 48, 49, 50, 51 or 52.

25. A cynomolgus VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOS: 88, 89, 90, 91, 92 or 93.

26. A cynomolgus V_K acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOS: 59, 60, 61, 62, 63 or 64.

27. A cynomolgus V_K acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOS: 94, 95 or 96.

28. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOS: 10, 11, 12, 13, 14, 15, 16, 17, 18, 28, 29, 30, 31, 32, 33, 34, 35 or 36.

29. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOS: 81, 82, 83, 84, 85, 86 or 87.

30. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOS: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or 64.

31. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOS: 88, 89, 90, 91, 92, 93, 94, 95 or 96.

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Figure 1

4A6 DTVLTQSPA. LAVPPGERVT VSCRASESVS TFLHWYQQKP GHQP
C108G AVHMTQSPSS LSASVGDSVT ITCRASQTIN IYLNWYQQKP GKAP

* *

4A6 KLLIYLASKL ESGVPARFSG GGSGTDFTLT IDPVEADDTA TYYCQQTWND
C108G KLLIFDASIL QSGVPSRFSG SGSGTDFSLT IRSLOPEDFA TYYCQCWGUTH

4A6 PRTFGCGT KLELKR
C108G PYNFGQGT KLEIKR

Figure 2

4A6 EVQLQQSGPE VGRPGSSVKI SCKASGYTFT **DYVLMNK** QSPGQGLEWI
C108G EVQLVESGGG VVQPGGSLRL SCAASGFTFD **DFAMEHWR** QAPGKGLEWI

* * * * *
4A6 **GWIDPDYG TTDYAEKFKK** KATLTADTSS STAYIQLSSL TSEDTATYFC
C108G **SLVSWDSY NIYHADSVKG** RFTISRDNSR NSLYLQMNDL RPEDTAIYFC

*
4A6 **ARSRYGG.. YI NYWGQGVMTVS**
C108G **AKADTGDDFD YVSDSWRCAL DYWGQGTLVTVS**

Figure 3

	1	<i>CDR1</i>
VLB9 Cmp46-3	DIQMTQTTSS LSASLGDRV T ITC <u>RSSQ</u> <i>DISNFLN</i> WYQQKPDGTV	
	DIQMTQSPSS LSASVGDRV T ITC <u>RASQ</u> <i>GISNYLA</i> WYQQKPGKAP	
	45 <i>CDR2</i>	<i>CDR3</i> 94
VLB9 Cmp46-3	KLLIYYT <u>STL</u> HSGVPSRFSG SGSGTDYSLT ISNLEQEDIA TYFC <u>QQGNTL</u>	
	KLLIYY <u>ASRL</u> ESGVPSRFSG SGSGTDYTLT ISSLQPEDFA TYYC <u>QQYNSN</u>	
	95	
VLB9 cmp46-1	<i>P..WTFGGGT</i> NLEIKR	
	FGGGT KVEIKR	

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Figure 4

	1	11	21	CDR1	39	48
				*	*	*
VHB9	QVQLQQSGAE	LMKPGASVKI	SCKATGYTFS	SYWIE..WVK	QRPGHGLEWI	
AMP41CL18	QVQLVQSGAE	VKKPGSSVKV	SCKVSGGTFS	TYGFS..WVR	QAPGQGLEWM	
	49	CDR2	66	76	83	92
			*	*	*	
VHB9	GEILP..RSG	NTNYNEKFKG	KATFTAETSS	NTAYMQLSSL	TPEDSAVYYC	
AMP41CL18	GMIIP..IVG	TVKYAQRFQG	RVSINADTST	NIAYMELTSL		
	RSEDTAVYYC					
	93	CDR3	104			
		*	*			
VHB9	SSRGVRGSM.....	DYW	GQGTSVTVSS			
AMP41CL18	ATDLTVTTNDAF.....	DI				
AMP41CL10			W	GQGTLVTVSS		

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Figure 5

VL3G9	1	CDR1	
*			
VK46-14	DIVMTQSQKF MSTSVGDRVS VTC KASQ NVGTNVA WYQQKPGQSP DIQMTQSPSS LSASVGDRV T ITC RASQ SISNYLS WYQQKPGKAP		
45 CDR2		CDR3 94	
* *			
VL3G9	KALIY SASYR YSGVPDRFTG SGSGTDFTLT ISNVQSEDLA EYFC QQYNSY		
VK46-14	KLLIY YASTL QSGVPSRFSG SGSGTDFTLT ISSLQPEDFA TYYC QEHYGT		
95			
VL3G9	P..LTFGAGT KLELK		
VK46-14	H..PTFGGGT KVEIK		

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Figure 6

1	11	21	CDR1	39	48
VH3G9	QVQLQQPGAE	LVKSGASVKL	SCKASGSTFT	SYWMH..WVK	QRPGRGLEWI
Chimp41-18	QVOLVQSGAE	VKKPGSSVKV	SCKVSGGTFS	TYGES..WVR	QAPGQGLEWM
49	CDR2	66	76	83	92
VH3G9	GRIDP..NSG	GTKDNEKFKS	KATLTVDKPS	STAYMQLSSL	TSEDSAVYYC
Chimp41-18	GMIIP..IVG	TVKYAQRFQG	RVSINADTST	NIAYMELTSL	RSEDTAVYYC
93	CDR3	104			
VH3G9	ARETYYDSS.....	FAYW	GQGTLVTVS		
Chimp41-18	ATDLTVTTN.....	DAFDIW	GQGTMVTVS		

SEQUENCE LISTING

<110> Taylor, Alexander H

<120> Monoclonal Antibodies with Reduced
Immunogenicity

<130> P50770

<150> 60/083,367

<151> 1998-04-28

<160> 97

<170> FastSEQ for Windows Version 3.0

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<212> DNA

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<220>

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Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

48

gtc ctg tcc cag gtg cag ttg cag gag tcg ggc cca gga ctg gtg aag
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

96

cct tca cag acc ttg tcc ctg acc tgc gct gtg tct ggt ggc tcc atc
Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile

144

35	40	45	
			192
act agt gct tac tac tat tgg agc tgg atc cgc cag tca cca ggg aag			
Thr Ser Ala Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys			
50	55	60	
			240
gga ctg gag tgg att ggg agt atc tat tat agt ggg acc att ttc tcc			
Gly Leu Glu Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Thr Ile Phe Ser			
65	70	75	80
aac cca tcc ctc aag agt cga gtc gcc atg tca gta ggc acg tcc aag			
Asn Pro Ser Leu Lys Ser Arg Val Ala Met Ser Val Gly Thr Ser Lys			
85	90	95	
			288
acc cag ttc tcc ctg agc ttg agt tct gtg acc gcc gcg gac acg gcc			
Thr Gln Phe Ser Leu Ser Ser Val Thr Ala Ala Asp Thr Ala			
100	105	110	
			336
gtg tac tac tgt gcg aga ggt ctg ctc acc att gga ctg acc aac			
Val Tyr Tyr Cys Ala Arg Gly Leu Leu Leu Thr Ile Gly Leu Thr Asn			
115	120	125	
			384
tac tac ttt gac tac tgg ggc ccg gga acc ctg gtc acc gtc ttc			
Tyr Tyr Phe Asp Tyr Trp Gly Pro Gly Thr Leu Val Thr Val Phe			
130	135	140	
			429

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Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp			
1	5	10	15
gtc ctg tcc cag gtg cag cta cag gag tcg ggc cca gga cta gtg aag			96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys			
20	25	30	
ccg tca cag acc ctg tcc ctc acc tgc ggt gtc tct ggt gcc tcc atc			144
Pro Ser Gln Thr Leu Ser Leu Thr Cys Gly Val Ser Gly Ala Ser Ile			
35	40	45	
aat agt ggt gtt cat tac tgg gcc tgg ata cgc cag cct gca gga aag			192
Asn Ser Gly Val His Tyr Trp Ala Trp Ile Arg Gln Pro Ala Gly Lys			
50	55	60	
gga ctg gag tgg att ggc aat atc tat cat agt ggg agc gcc tac tac			240
Gly Leu Glu Trp Ile Gly Asn Ile Tyr His Ser Gly Ser Ala Tyr Tyr			
65	70	75	80
act cca tcc ctc gag agt cga gtc tcc atg tca ata gag acg tcc aag			288
Thr Pro Ser Leu Glu Ser Arg Val Ser Met Ser Ile Glu Thr Ser Lys			
85	90	95	
agc cag ttc ttc cta aac tta aat tct ctg acc gcc gcg gac acg gct			336
Ser Gln Phe Phe Leu Asn Leu Asn Ser Leu Thr Ala Ala Asp Thr Ala			
100	105	110	
atc tat tat tgt gcg aga cga cat act tcg tca gac tac ttt gac ttt			384
Ile Tyr Tyr Cys Ala Arg Arg His Thr Ser Ser Asp Tyr Phe Asp Phe			
115	120	125	
tgg ggc cgc gga atc ctg gtc atc gtc tcc			414
Trp Gly Arg Gly Ile Leu Val Ile Val Ser			
130	135		

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Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Glu Gly				
1	5	10	15	
gtc cgt gca gac gtg cag ctg gtg cag tcc gga gca gag gtg aaa aag				96
Val Arg Ala Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys				
20	25	30		
ccc ggg gag tct ctg aag atc tcc tgt aag gtc tct gga aat gaa ttt				144
pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Asn Glu Phe				
35	40	45		
acc aac tac tgg atc gcc tgg gtg cgc cag atg tcc ggg aaa ggc ctg				192
Thr Asn Tyr Trp Ile Ala Trp Val Arg Gln Met Ser Gly Lys Gly Leu				
50	55	60		
gag tgg atg ggg agc atc tat cct ggt gac tct gat acc aga tac aac				240
Glu Trp Met Gly Ser Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Asn				
65	70	75	80	
ccg tcc ttc caa ggc caa gtc acc ttt tca gcc gac aag tcc atc acc				288
Pro Ser Phe Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Thr				
85	90	95		
acc gcc tat ttg cag tgg agt agt ctg gag gcc tcg gac acc gcc atg				336
Thr Ala Tyr Leu Gln Trp Ser Ser Leu Glu Ala Ser Asp Thr Ala Met				
100	105	110		

tac tac tgt gcg agc cga aat cac ttt gtt ttc ggg gaa gtt att act			384
Tyr Tyr Cys Ala Ser Arg Asn His Phe Val Phe Gly Glu Val Ile Thr			
115	120	125	
act ttg acg gct ggg gcc agg gaa acc ctg ggt cac cgt ctc c			427
Thr Leu Thr Ala Gly Ala Arg Glu Thr Leu Gly His Arg Leu			
130	135	140	
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Leu Gly Leu Arg Trp Val Phe Leu Val Ala Phe Leu Glu Gly Val Gln			
1	5	10	15
tgt gag gta cag ctg gtg gag tct ggg gga ggc ttg gta cag cct ggg			96
Cys Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly			
20	25	30	
ggg tcc ttg aca ctc tcc tgt gca gcc tct gga ttc acc ttc agt agg			144
Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg			
35	40	45	
agt ggc atg cac tgg gtc cgc cag gct cca ggg aag gga ctg ggg tgg			192
Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gly Trp			
50	55	60	
ctt gca tac att gat tat ggc agt att ttc ata tac tac tcg gac tca			240
Leu Ala Tyr Ile Asp Tyr Gly Ser Ile Phe Ile Tyr Tyr Ser Asp Ser			

65	70	75	80	
				288
gtg aag ggc cgc ttc acc atc tcc aga gac aac gcc aag aat tca ctc Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu				
85		90		95
				336
tat ctg caa atg aac agc ctg aga gcc gac gac acg gct ttt tat tac Tyr Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Phe Tyr Tyr				
100		105		110
				384
tgt acg acc cat aat tgg ggg gag tta act gac tac tgg ggc cag gga Cys Thr Thr His Asn Trp Gly Glu Leu Thr Asp Tyr Trp Gly Gln Gly				
115		120		125
				402
acc ctg gtc acc gtc tcc Thr Leu Val Thr Val Ser				
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1	5	10		15
				96
gtc cag tgt gag gta cag ctg gtg gag tct ggg gga ggc ttg gta cag Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln				
20		25		30

cct	ggg	ggg	tcc	ttg	aca	ctc	tcc	tgt	gca	gcc	tct	gga	ttc	acc	ttc		144
Pro	Gly	Gly	Ser	Leu	Thr	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe		
35															45		
agt	agg	agt	ggc	atg	cac	tgg	gtc	cgc	cag	gct	cca	ggg	aag	gga	ctg		192
Ser	Arg	Ser	Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu		
50															60		
gag	tgg	ctt	gca	tac	att	gat	tat	ggc	agt	att	ttc	ata	tac	tac	tcg		240
Glu	Trp	Leu	Ala	Tyr	Ile	Asp	Tyr	Gly	Ser	Ile	Phe	Ile	Tyr	Tyr	Ser		
65															80		
gac	tca	gtg	aag	ggc	cgc	ttc	acc	atc	tcc	aga	gac	aac	gcc	aag	aat		288
Asp	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn		
85															95		
tca	ctc	tat	ctg	caa	atg	aac	agc	ctg	aga	gcc	gac	gac	acg	gct	ttt		336
Ser	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Asp	Asp	Thr	Ala	Phe		
100															110		
tat	tac	tgt	acg	acc	cat	aat	tgg	ggg	gag	tta	act	gac	tac	tgg	ggc		384
Tyr	Tyr	Cys	Thr	Thr	His	Asn	Trp	Gly	Glu	Leu	Thr	Asp	Tyr	Trp	Gly		
115															125		
cag	gga	acc	ctg	gtc	acc	gtc	tcc										408
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser										
130																	

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 gga gtc tgt gca gag gtg cag ctg gtg cag tct gga gca gag gtg aaa	96
Gly Val Cys Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys	
20 25 30	
 aag ccc ggg gag tct ctg aag atc tcc tgt aag ggc tct gga tac agt	144
Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser	
35 40 45	
 ttt acc aac tac tgg atg ggc tgg gtg tgc cag atg ccc ggg aaa ggc	192
Phe Thr Asn Tyr Trp Met Gly Trp Val Cys Gln Met Pro Gly Lys Gly	
50 55 60	
 ccg gag tgc atg ggg atc atc tat cct gat gac tct gat acc aga tac	240
Pro Glu Cys Met Gly Ile Ile Tyr Pro Asp Asp Ser Asp Thr Arg Tyr	
65 70 75 80	
 agc ccg tcc ttccaa ggc cag gtc acc atc tca gcc gac aag tcc atc	288
Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile	
85 90 95	
 agc acc gcc tac cta caa tgg agc aac ctg aag gcc tcg gac acc gcc	336
Ser Thr Ala Tyr Leu Gln Trp Ser Asn Leu Lys Ala Ser Asp Thr Ala	
100 105 110	
 ata tat tac tgt gcg aga tgt tat ggt tgg act act tgc gaa gct ttt	384
Ile Tyr Tyr Cys Ala Arg Cys Tyr Gly Trp Thr Thr Cys Glu Ala Phe	
115 120 125	
 gat atc tgg ggc caa ggg aca atg gtc acc gtc tct t	421
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser	
130 135 140	

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Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 100 105 110

tgt gcg aga tct ccc caa aac gta tta caa tct ttg gac tgc ttc gac 384
 Cys Ala Arg Ser Pro Gln Asn Val Leu Gln Ser Leu Asp Cys Phe Asp
 115 120 125

ccc tgg ggc cag gga acc ctg gtc acc gtc tcc 417
 Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 130 135

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 Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
 1 5 10 15

cct ggg tcc tca gtg aag gtc tcc tgc aag gtt tcc gga ggc acc ttc 96
 Pro Gly Ser Ser Val Lys Val Ser Cys Lys Val Ser Gly Gly Thr Phe
 20 25 30

agc acc tat ggt ttc agc tgg gtg cgg cag gcc cct gga caa ggg ctt 144
 Ser Thr Tyr Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
 35 40 45

gag tgg atg gga atg atc atc cct atc gtt ggc aca gta aag tac gca 192
 Glu Trp Met Gly Met Ile Ile Pro Ile Val Gly Thr Val Lys Tyr Ala
 50 55 60
 10

cag agg ttc cag ggc aga gtc tca att aat gcg gac aca tcc acg aat	240		
Gln Arg Phe Gln Gly Arg Val Ser Ile Asn Ala Asp Thr Ser Thr Asn			
65	70	75	80
ata gcc tac atg gag ctg acc agc ctg aga tct gag gac acg gcc gtc	288		
Ile Ala Tyr Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val			
85	90	95	
tat tac tgt gcg aca gat ctg acg gtg act act aat gat gca ttt gat	336		
Tyr Tyr Cys Ala Thr Asp Leu Thr Val Thr Thr Asn Asp Ala Phe Asp			
100	105	110	
atc tgg ggc caa ggg aca atg gtc acc gtc tct	369		
Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser			
115	120		
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1	5	10	15
gtc cag tgt gag gtg cag ctg gtg gag tct ggg gaa ggc ttg gta aag	96		
Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Glu Gly Leu Val Lys			
20	25	30	
cct ggg ggt tcc ctg aga ctc tcg tgt gca gcc tct gga ttc acc ttc	144		

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe			
35	40	45.	
agt agt ttt ctt atg ttc tgg gtc cgc cag gct cca gaa aag ggg ctg			192
Ser Ser Phe Leu Met Phe Trp Val Arg Gln Ala Pro Glu Lys Gly Leu			
50	55	60	
gag tgg gtc tca act att gat gtt agt ggt aat atg tgg tac cga			240
Glu Trp Val Ser Thr Ile Asp Val Ser Gly Gly Asn Met Trp Tyr Arg			
65	70	75	80
gac tct gtc aag ggc cga ttc acc atg tcc aga gac aat tcc aag aac			288
Asp Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn			
85	90	95	
aca ctg tat ctg caa atg acc agc ctg aga gcc gac gac acg gcc gtt			336
Thr Leu Tyr Leu Gln Met Thr Ser Leu Arg Ala Asp Asp Thr Ala Val			
100	105	110	
tac tat tgt gcg aga gag gga cga gac cct agc ggc act tgg gga tac			384
Tyr Tyr Cys Ala Arg Glu Gly Arg Asp Pro Ser Gly Thr Trp Gly Tyr			
115	120	125	
ttt gac tac tgg ggc cag gga atc ctg gtc acc gtc tcc			423
Phe Asp Tyr Trp Gly Gln Gly Ile Leu Val Thr Val Ser			
130	135	140	

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20 25 30
Tyr Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu
35 40 45
Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Thr Ile Phe Ser Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Ala Met Ser Val Gly Thr Ser Lys Thr Gln Phe
65 70 75 80
Ser Leu Ser Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys

<210> 11

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Thr Leu Ser Leu Thr Cys Gly Val Ser Gly Ala Ser Ile Asn Ser Gly			
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Val His Tyr Trp Ala Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu			
35		40	45
Trp Ile Gly Asn Ile Tyr His Ser Gly Ser Ala Tyr Tyr Thr Pro Ser			
50		55	60
Leu Glu Ser Arg Val Ser Met Ser Ile Glu Thr Ser Lys Ser Gln Phe			
65		70	75
Phe Leu Asn Leu Asn Ser Leu Thr Ala Asp Thr Ala Ile Tyr Tyr Cys			
85		90	95

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20		25	30
Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Asn Glu Phe Thr Asn Tyr			
35		40	45
Trp Ile Ala Trp Val Arg Gln Met Ser Gly Lys Gly Leu Glu Trp Met			
50		55	60
Gly Ser Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Asn Pro Ser Phe			
65		70	75
Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr			
80			

Leu Gln Trp Ser Ser Leu Glu Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

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20 25 30
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35 40 45
Gly Ser Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Asn Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Glu Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

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1				5						10					15
Ser	Leu	Thr	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Arg	Ser
					20					25					30
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Gly	Trp	Leu
					35				40						45
Ala	Tyr	Ile	Asp	Tyr	Gly	Ser	Ile	Phe	Ile	Tyr	Tyr	Ser	Asp	Ser	Val
		50				55				60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
	65					70				75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Asp	Asp	Thr	Ala	Phe	Tyr	Tyr	Cys
					85					90					95

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 20 25 30
 Trp Met Gly Trp Val Cys Gln Met Pro Gly Lys Gly Pro Glu Cys Met
 35 40 45
 Gly Ile Ile Tyr Pro Asp Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Asn Leu Lys Ala Ser Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95

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 20 25 30
 Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Arg Leu Glu
 35 40 45
 Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60
 Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe

65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95
Cys

<210> 17
<211> 96
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (31)...(35)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 17
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Val Ser Gly Gly Thr Phe Ser Thr Tyr
 20 25 30
Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
Gly Met Ile Ile Pro Ile Val Gly Thr Val Lys Tyr Ala Gln Arg Phe
 50 55 60
Gln Gly Arg Val Ser Ile Asn Ala Asp Thr Ser Thr Asn Ile Ala Tyr
65 70 75 80
Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

<210> 18
<211> 96
<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 18

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Glu	Gly	Leu	Val	Lys	Pro	Gly	Gly
1															
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Phe
			20					25			30				
Leu	Met	Phe	Trp	Val	Arg	Gln	Ala	Pro	Glu	Lys	Gly	Leu	Glu	Trp	Val
			35					40			45				
Ser	Thr	Ile	Asp	Val	Ser	Gly	Gly	Asn	Met	Trp	Tyr	Arg	Asp	Ser	Val
			50			55			60						
Lys	Gly	Arg	Phe	Thr	Met	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
			65			70			75			80			
Leu	Gln	Met	Thr	Ser	Leu	Arg	Ala	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
							85		90			95			

<210> 19

<211> 381

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(381)

<400> 19

atg	agg	gtc	cct	gct	cag	ctg	ggg	ctc	ctg	ctg	ctc	tgg	ctc	tca
Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Trp	Leu	Ser

48

1	5	10	15	
				96
ggt gcc aga tgt gac atc cag atg acc cag ttt cca tcc tcc ctg tct Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Phe Pro Ser Ser Leu Ser				
20		25		30
				144
gca tct gta gga gac aga gtc acc atc act tgc cag tca agt cag agc Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser				
35		40		45
				192
att tac aac tgc ttg agt tgg tat cag cag aaa cca ggg aag gcc cct Ile Tyr Asn Cys Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro				
50		55		60
				240
aca ctc cta atc tat ggt gca ttc acc ttg aat agt ggg gtc cca tca Thr Leu Leu Ile Tyr Gly Ala Phe Thr Leu Asn Ser Gly Val Pro Ser				
65		70		75
				288
aga ttc agt ggc agt gga tct ggc aca gat ttc act ctc acc atc agc Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser				
85		90		95
				336
aat ctg caa cct gaa gat ttt gca aca tat tac tgt cag cgt ggt tac Asn Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Arg Gly Tyr				
100		105		110
				381
ggc aca cag ctc act ttc ggt gga ggg acc aag gtg gag atc aag Gly Thr Gln Leu Thr Phe Gly Gly Thr Lys Val Glu Ile Lys				
115		120		125

<210> 20
<211> 384
<212> DNA
<213> Pan troglodytes

<220>

<221> CDS

<222> (1) ... (384)

<400> 20 atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp 1 5 10 15	48
ctc cca ggt acc aga tgt gac atc cag atg acc cag tct cca tcc tcc Leu Pro Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser 20 25 30	96
ctg tct gca tct gta gga gac aga gtc acc atc act tgc cgg gcc agt Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser 35 40 45	144
cag ggc att agc aat tat tta gcc tgg tat cag cag aaa cca ggg aaa Gln Gly Ile Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys 50 55 60	192
gcc cct aag ctc ctc atc tat tat gca tcc aga ttg gaa agt ggg gtc Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Arg Leu Glu Ser Gly Val 65 70 75 80	240
cca tca agg ttc agc ggc agt gga tct ggg acg gat tac act ctc acc Pro Ser Arg Phe Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr 85 90 95	288
atc agc agc ctg cag cct gaa gat ttt gca act tat tac tgt caa cag Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln 100 105 110	336
tat aac agt aac ccc ttt tcg gtg gag gga cca agg tgg aga tca aac Tyr Asn Ser Asn Pro Phe Ser Val Glu Gly Pro Arg Trp Arg Ser Asn 115 120 125	384

<210> 21
 <211> 384
 <212> DNA
 <213> Pan troglodytes

<220>
 <221> CDS
 <222> (1)...(384)

<400> 21

atg	tcg	cca	tca	caa	ctc	att	ggg	ttt	ctg	ctg	ctc	tgg	gtt	cca	gcc	48
Met	Ser	Pro	Ser	Gln	Leu	Ile	Gly	Phe	Leu	Leu	Leu	Trp	Val	Pro	Ala	
1															15	

tcc agg ggt gaa att gtg ctg act cag tct cca gac ttt cag tct gtg

Ser	Arg	Gly	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Asp	Phe	Gln	Ser	Val	96
20																

25

30

cct cca aag gag aaa gtc acc atc acc tgc cgg gcc agt cag agc att

Pro	Pro	Lys	Glu	Lys	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	144
35																

40

45

ggt agt agc tta cac tgg tac cag cag aaa cca ggt cag tct cca aag

Gly	Ser	Ser	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Lys	192
50																

55

60

ctc ctc atc aag tat gct tcc cag tcc atc tca ggg gtc ccc tcg agg

Leu	Leu	Ile	Lys	Tyr	Ala	Ser	Gln	Ser	Ile	Ser	Gly	Val	Pro	Ser	Arg	240
65																

70

75

80

ttc agt ggc agt gga tct ggg aca gat ttc acc ctc acc atc aat agc

Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asn	Ser	288
85																

90

95

ctg gaa gct gaa gat gct gca acg tat tac tgt cag caa agt agt aat

Leu	Glu	Ala	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ser	Asn	336
100																

105

110

22

tta cct cat acg ctc act ttc ggt gga ggg acc aag gtg gag atc aaa				384
Leu Pro His Thr Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys				
115	120	125		
<210> 22				
<211> 372				
<212> DNA				
<213> Pan troglodytes				
<220>				
<221> CDS				
<222> (1)...(372)				
<400> 22				
gtc cct gct cag ctc ctg ggg ctc ctg ctc tgg ctc tca ggt gcc				48
Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Ser Gly Ala				
1	5	10	15	
aga tgt gac atc cag atg acc cag tct cca tcc tcc ctg tct gca tct				96
Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser				
20	25	30		
gta gga gac aga gtc acc atc act tgc cag gca agt cag agc att agc				144
Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser				
35	40	45		
aac tat ttg agt tgg tat cag cag aaa cca ggg aaa gcc cct aag ctc				192
Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu				
50	55	60		
ctg atc tat gat gca tcc act ttg caa agt ggg gtc cca tca agg ttc				240
Leu Ile Tyr Asp Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe				
65	70	75	80	
agt ggc agt gga tct ggg aca gat ttc act ctc acc atc agc agt ctg				288

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu		
85	90	95
caa cct gaa gat ttt gca aca tat tac tgt cag cgt ggt tac ggt aca		
Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Arg Gly Tyr Gly Thr		
100	105	110
ctc act ttc ggt gga ggg acc aag gtg gag atc aaa		
Leu Thr Phe Gly Gly Thr Lys Val Glu Ile Lys		
115	120	
<210> 23		
<211> 384		
<212> DNA		
<213> Pan troglodytes		
<220>		
<221> CDS		
<222> (1)...(384)		
<400> 23		
atg gaa gcc cca gcg cag ctt ctc ttc ctc ctg cta ctc tgg ctc cca		
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Trp Leu Pro		
1	5	10
		15
gat acc acc gga gaa ata gtg ttg acg cag tct cca gcc acc ctg tct		
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser		
20	25	30
ttg tct cca ggg gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt		
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser		
35	40	45
gtt agc agg tac tta gcc tgg tac cag cag aaa cct ggc cag gct ccc		
Val Ser Arg Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro		
50	55	60
		192
		336
		48
		96
		144

agg ctc ctc atc tat ggt gca tcc aac agg gcc act ggc atc cca gcc 240
 Arg Leu Leu Ile Tyr Gly Ala Ser Asn Arg Ala Thr Glu Ile Pro Ala
 65 70 75 80

agg ttc agt ggc agt ggg tct agg aca gac ttc act ctc acc atc agc 288
 Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
 85 90 95

agc gtg gag cct gaa gat ttt gca gtt tat tac tgt cag cag tat aat 336
 Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn
 100 105 110

aac cag cct ctg atc gcc ttc ggc caa ggg aca cga ctg gag att aaa 384
 Asn Gln Pro Leu Ile Ala Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 115 120 125

<210> 24
<211> 387
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(387)

<400> 24
atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg 48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp
 1 5 10 15

ttc cca ggt gcc aaa tgt gac atc cag atg acc cag cag tct cct tcc acc 96
Phe Pro Gly Ala Lys Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
 20 25 30

ctg tct gcc tcc ata gga gac aga gtc acc atc act tgt cgg gct agt 144
 25

Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser 35	40	45	
 cag ggc atc tat aat tat ttg aat tgg tat cag caa aaa cca ggg aga Gln Gly Ile Tyr Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Arg 50			192
 gcc cct gga ctc ctc atc ttt ggt gcc agg aat ttg gag act ggg gtc Ala Pro Gly Leu Leu Ile Phe Gly Ala Arg Asn Leu Glu Thr Gly Val 65			240
 cca tca aca ttc agc ggc agt ggt tcc ggg aca cac ttc act ctc acc Pro Ser Thr Phe Ser Gly Ser Gly Thr His Phe Thr Leu Thr 85			288
 atc agc agc ctg cag cct ggt gat ttt gcg act tat tac tgt cag caa Ile Ser Ser Leu Gln Pro Gly Asp Phe Ala Thr Tyr Tyr Cys Gln Gln 100			336
 tat tat act acc ccg tat act ttt ggc cag ggg acc aag ctg gag atc Tyr Tyr Thr Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile 115			384
 aaa			387
 <210> 25			
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<212> DNA			
<213> Pan troglodytes			
 <220>			
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<222> (1)...(387)			
 <400> 25			
atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgt Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Cys			48

1	5	10	15	
				96
ttc cca ggt gcc aga tgt gac atc cag atg acc cag cag tct cca tcc tca Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser				
20		25		30
				144
ctg tct gct tct gta gga gac aga gtc acc atc tct tgt cgg gcg agt Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser				
35		40		45
				192
ctg gat att agc acc tgg tta gcc tgg tat cag cag aaa cca ggg aaa Leu Asp Ile Ser Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys				
50		55		60
				240
gcc cct aag ccc ctg atc tat gct gca tcc act ttg cca agt ggg gtc Ala Pro Lys Pro Leu Ile Tyr Ala Ala Ser Thr Leu Pro Ser Gly Val				
65		70		75
				80
cca tcg agg ttc agc ggc agt gga tct ggg aca gat ttc act ctc acc Pro Ser Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr				
85		90		95
				288
atc agc agc ctg cag cct gaa gat tct gca act tat tac tgc cga caa Ile Ser Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Arg Gln				
100		105		110
				336
tat aat agt tat ccg ctc act ttc ggt gga ggg acc aag gtg gag atc Tyr Asn Ser Tyr Pro Leu Thr Phe Gly Gly Thr Lys Val Glu Ile				
115		120		125
				384
aag				387
<210> 26				
<211> 372				
<212> DNA				
<213> Pan troglodytes				

<220>

<221> CDS

<222> (1)...(372)

<400> 26

tct act cag ctc ctg ggg ctc ctg ctg ctc tgg ctc cca ggt gcc aaa	48		
Ser Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Pro Gly Ala Lys			
1	5	10	15

tgt gac atc cag atg acc cag tct cct tcc acc ctg tct gca tct gta	96		
Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val			
20	25	30	

gga gac aga gtc acc atc act tgc cgg gcc agt cag ggt att agt agc	144		
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser			
35	40	45	

tgg tta gcc tgg tat cag cag aaa cca ggg aaa gcc cct aag ctc ctg	192		
Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu			
50	55	60	

atc tat aag gca tct agt tta gaa agt ggg gtc cca tca agg ttc agc	240		
Ile Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser			
65	70	75	80

ggc agt gga tct ggg aca gaa ttc act ctc acc atc agc agc ctg cag	288		
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln			
85	90	95	

cct gat gat ttt gca act tat tac tgc caa cag tat agt agt tac cct	336		
Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro			
100	105	110	

cga acg ttc ggc caa ggg acc aag ctg gaa atc aaa	372	
Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys		
115	120	

<210> 27
 <211> 387
 <212> DNA
 <213> Pan troglodytes

<220>
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 <222> (1) ... (387)

<400> 27

atg	gac	atg	agg	gtc	ccc	gct	cag	ctc	ctg	ggg	ctc	ctg	ctg	ctc	tgg	48
Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp	
1		5							10					15		

ctc	tca	ggt	acc	aga	tgt	gac	atc	cag	atg	acc	cag	tct	cca	tcc	tcc	96
Leu	Ser	Gly	Thr	Arg	Cys	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	
							20		25				30			

ctg	tct	gca	tct	gta	gga	gac	aga	gtc	acc	atc	act	tgc	cgg	gca	agt	144
Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	
							35		40			45				

cag	agc	att	agc	aac	tat	ttg	agt	tgg	tat	cag	cag	aaa	cca	ggg	aaa	192
Gln	Ser	Ile	Ser	Asn	Tyr	Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	
						50		55			60					

gcc	cct	aag	ctc	ctg	atc	tat	tat	gca	tcc	act	ttg	caa	agt	ggg	gtc	240
Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Tyr	Ala	Ser	Thr	Leu	Gln	Ser	Gly	Val	
						65		70			75		80			

cca	tca	agg	ttc	agt	ggc	agt	gga	tct	ggg	aca	gat	ttc	act	ctc	acc	288
Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	
							85		90			95				

atc	agc	agt	ctg	caa	cct	gaa	gat	ttt	gca	act	tat	tac	tgt	cag	cat	336
Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	

100	105	110	
			384
ggt tac ggt aca cat ccc act ttc ggt gga ggg acc aag gtg gag atc			
Gly Tyr Gly Thr His Pro Thr Phe Gly Gly Thr Lys Val Glu Ile			
115	120	125	
			387
aaa			
<210> 28			
<211> 88			
<212> PRT			
<213> Pan troglodytes			
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<221> DOMAIN			
<222> (24)...(34)			
<223> CDRI			
<221> DOMAIN			
<222> (50)...(66)			
<223> CDRII			
<400> 28			
Asp Ile Gln Met Thr Gln Phe Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15
Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser Ile Tyr Asn Cys			
20	25	30	
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Thr Leu Ile			
35	40	45	
Tyr Gly Ala Phe Thr Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly			
50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro			
65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys			
85			
<210> 29			
30			

<211> 88
<212> PRT
<213> Pan troglodytes

<220>
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<222> (24) . . . (34)
<223> CDRI

<221> DOMAIN
<222> (50) . . . (66)
<223> CDRII

<400> 29

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Arg Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys
85

<210> 30
<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24) . . . (34)
<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 30

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Pro Pro Lys
1 5 10 15
Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45
Lys Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
65 70 75 80
Glu Asp Ala Ala Thr Tyr Tyr Cys
85

<210> 31

<211> 88

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 31

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser Asn Tyr
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys
 85

<210> 32

<211> 88

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (24) ... (34)

<223> CDRI

<221> DOMAIN

<222> (50) ... (66)

<223> CDRII

<400> 32

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Arg Tyr
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Gly Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys
 85

<210> 33
<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24) . . . (34)
<223> CDRI

<221> DOMAIN
<222> (50) . . . (66)
<223> CDRII

<400> 33

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Tyr Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Gly Leu Leu Ile
35 40 45
Phe Gly Ala Arg Asn Leu Glu Thr Gly Val Pro Ser Thr Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr His Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Gly Asp Phe Ala Thr Tyr Tyr Cys
85

<210> 34
<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24) . . . (34)
<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 34

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Leu Asp Ile Ser Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Pro Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ser Ala Thr Tyr Tyr Cys
85

<210> 35

<211> 88

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 35

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
35

20	25	30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
35	40	45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
65	70	75
Asp Asp Phe Ala Thr Tyr Tyr Cys		
	85	

<210> 36
 <211> 88
 <212> PRT
 <213> Pan troglodytes

<220>
 <221> DOMAIN
 <222> (24)...(34)
 <223> CDRI

<221> DOMAIN
 <222> (50)...(66)
 <223> CDRII

<400> 36		
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly		
1	5	10
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr		
20	25	30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
35	40	45
Tyr Tyr Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
65	70	75
Glu Asp Phe Ala Thr Tyr Tyr Cys		
	85	

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<210> 37
<211> 408
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(408)

<400> 37
atg gag ttt gga ctg agc tgg gtt ttc ctt gtc gct att ttc aaa ggt      48
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Phe Lys Gly
1           5           10          15

gtc cag tgt gaa gtg cag ttg gtg gag tct ggg gga ggc ttg gta cag      96
Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln
20          25          30

ccg ggg ggg tcc ctg aga ctc gcc tgt gta ggc tct gga ttc gcc ttc      144
Pro Gly Gly Ser Leu Arg Leu Ala Cys Val Gly Ser Gly Phe Ala Phe
35          40          45

aga aac acc agg atg cac tgg att cga cag act cca gga aag agg ctg      192
Arg Asn Thr Arg Met His Trp Ile Arg Gln Thr Pro Gly Lys Arg Leu
50          55          60

gag tgg gtg gcc gac ata aag ttt gat gga agt gat ttt tac tat gta      240
Glu Trp Val Ala Asp Ile Lys Phe Asp Gly Ser Asp Phe Tyr Tyr Val
65          70          75          80

gac tct gtg aag ggc cga ttc acc atc tcc aga gac aac gcc aag aac      288
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85          90          95

tcc ctc tat ctg gaa atg aac agc ctg aga cct gat gac aca gcc gtc      336
Ser Leu Tyr Leu Glu Met Asn Ser Leu Arg Pro Asp Asp Thr Ala Val

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100	105	110	
tat ttc tgt gtg aga gaa tac aga gat gga ctg gat gtc tgg ggc cgg 384 Tyr Phe Cys Val Arg Glu Tyr Arg Asp Gly Leu Asp Val Trp Gly Arg			
115	120	125	
gga gtt ctg gtc acc gtc tcc tca 408 Gly Val Leu Val Thr Val Ser Ser			
130	135		
 <210> 38 <211> 381 <212> DNA <213> Macaca cynomolgus			
<220> <221> CDS <222> (1)...(381)			
<400> 38			
gtg aca gct ccc aga tgg gtc ctg tcc cag gtg caa ttg cag gag tcg 48 Val Thr Ala Pro Arg Trp Val Leu Ser Gln Val Gln Leu Gln Glu Ser			
1	5	10	15
ggc cca gga ctg gtg aag cct tcg gag acc ctg tcc ctc act tgt act 96 Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr			
20	25	30	
gtc tct ggt gac tcc atc acc act gtc ttc tgg agc tgg ctc cgc cag 144 Val Ser Gly Asp Ser Ile Thr Thr Val Phe Trp Ser Trp Leu Arg Gln			
35	40	45	
tcg cca ggg att ggg ctg gag tgg att ggg aat ttt gct ggt agt act 192 Ser Pro Gly Ile Gly Leu Glu Trp Ile Gly Asn Phe Ala Gly Ser Thr			
50	55	60	
38			

ccg gaa acg aac tac aat ccc tcc ctc aag aat cga gcc acc att tca				240
Pro Glu Thr Asn Tyr Asn Pro Ser Leu Lys Asn Arg Ala Thr Ile Ser				
65	70	75	80	
aaa gac acg ccc acg aat caa ttt ttc ctg agg ctg acg tct gtg acc				288
Lys Asp Thr Pro Thr Asn Gln Phe Phe Leu Arg Leu Thr Ser Val Thr				
85	90	95		
gcc gcg gac acg gcc gtc tac ttc tgt gcg aga gga ggg gga gcc ggc				336
Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala Arg Gly Gly Ala Gly				
100	105	110		
aac cca ctc act tgg ggc cag gga gtc cag gtc acc gtc tcc tca				381
Asn Pro Leu Thr Trp Gly Gln Gly Val Gln Val Thr Val Ser Ser				
115	120	125		
<210> 39				
<211> 417				
<212> DNA				
<213> Macaca cynomolgus				
<220>				
<221> CDS				
<222> (1)...(417)				
<400> 39				
atg ggg tca act gcc atc ctc gcc ctc ctc ctg gct gtt ctc caa gga				48
Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly				
1	5	10	15	
gtc tgt gcc gag gtg cat ctg gtg cag tct gga gca cag gtg aaa agg				96
Val Cys Ala Glu Val His Leu Val Gln Ser Gly Ala Gln Val Lys Arg				
20	25	30		
ccc ggg gaa tct ctg agg atc tcc tgt aag act tct gga tac acc ttt				144
Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe				

35	40	45	
			192
acc gac agc tgg atc agc tgg gtg cgc cag atg ccc ggg aaa ggc ctg			
Thr Asp Ser Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu			
50	55	60	
			240
gag tgg atg gga aac atc tat cct ggt gat tct gat tcc aga tac aac			
Glu Trp Met Gly Asn Ile Tyr Pro Gly Asp Ser Asp Ser Arg Tyr Asn			
65	70	75	80
ccg tcc ttc caa ggc cgc gtc act atc tca gtc gac aag tcc atc agt			
Pro Ser Phe Gln Gly Arg Val Thr Ile Ser Val Asp Lys Ser Ile Ser			
85	90	95	
			288
acc acc tac ctg cag tgg agc agc ctg aag gcc tcg gac act gcc aca			
Thr Thr Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Thr			
100	105	110	
			336
tat tac tgt gcg aag ata gat agc aac tac tac agc cgg ttc gaa gtc			
Tyr Tyr Cys Ala Lys Ile Asp Ser Asn Tyr Tyr Ser Arg Phe Glu Val			
115	120	125	
			384
tgg ggc ccc gga gtc atg gtc acc gtc tcc tca			
Trp Gly Pro Gly Val Met Val Thr Val Ser Ser			
130	135		
			417

<210> 40
 <211> 423
 <212> DNA
 <213> Macaca cynomolgus

<220>
 <221> CDS
 <222> (1)...(423)

<400> 40

atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca gct cct aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtc ctg tcc cag gtg cag ttg gag tcg ggc cca gga gtg gtg aag	96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Val Val Lys	
20 25 30	
cct tcg gag acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc ttc	144
Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe	
35 40 45	
agt act tac tac tgg aat tgg atc cgc cag ccc cca ggg aag gga ctg	192
Ser Thr Tyr Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu	
50 55 60	
gag tgg att gga tat atc ggt ggt ggt ggt cgc ccc aac tac aat	240
Glu Trp Ile Gly Tyr Ile Gly Gly Gly Arg Pro Asn Tyr Asn	
65 70 75 80	
tcc tcc ctc aag agt cgc atc acc ctg tca cta gac gcg tcc aag aac	288
Ser Ser Leu Lys Ser Arg Ile Thr Leu Ser Leu Asp Ala Ser Lys Asn	
85 90 95	
cag ttc tcc ctg aac ctg agc tct gtg acc gcc gcg gac acg gcc gtg	336
Gln Phe Ser Leu Asn Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val	
100 105 110	
tac tac tgt gcc aga gat cgg ggc tac ggt gcc agc aat gat gct ttt	384
Tyr Tyr Cys Ala Arg Asp Arg Gly Tyr Gly Ala Ser Asn Asp Ala Phe	
115 120 125	
gat ttc tgg ggc caa ggg ctc agg gtc acc gtc tct tca	423
Asp Phe Trp Gly Gln Gly Leu Arg Val Thr Val Ser Ser	
130 135 140	

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<210> 41
<211> 411
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(411)

<400> 41
atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca act cct aaa tgg      48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Thr Pro Lys Trp
 1           5           10          15

gtc ctg tcc cag gtg cag ttg cat gag tgc ggc cct gga ctg ctg aag      96
Val Leu Ser Gln Val Gln Leu His Glu Ser Gly Pro Gly Leu Leu Lys
 20          25          30

cct tcg gag acc ctg tcc ctc acc tgc aat gtc tcc ggt gac tcc ccc      144
Pro Ser Glu Thr Leu Ser Leu Thr Cys Asn Val Ser Gly Asp Ser Pro
 35          40          45

act aag tcc acg tgg aac tgg gtc cgc cag tcc cca ggg aag cca ctg      192
Thr Lys Ser Thr Trp Asn Trp Val Arg Gln Ser Pro Gly Lys Pro Leu
 50          55          60

gaa tgg att ggt cat gtc ggt tct ggt gga ggt ggc ccc gtt tac aac      240
Glu Trp Ile Gly His Val Gly Ser Gly Gly Gly Pro Val Tyr Asn
 65          70          75          80

gtc ttc ttg acg ggt cgc gtc tcc atg tct cta gac gct tca aag aag      288
Val Phe Leu Thr Gly Arg Val Ser Met Ser Leu Asp Ala Ser Lys Lys
 85          90          95

ctt ctc tcc ctg gcc tta gca tct gtg acc gcc gcc gac tcg gcc gtc      336
Leu Leu Ser Leu Ala Leu Ala Ser Val Thr Ala Ala Asp Ser Ala Val
100         105         110

42

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tat tac tgt gtc aga tcg acg gca tta ttt tcg ttg gat gtc tgg ggc 384
 Tyr Tyr Cys Val Arg Ser Thr Ala Leu Phe Ser Leu Asp Val Trp Gly
 115 120 125

cgg gga ctt ctg gtc acc gtc tcc tca 411
Arg Gly Leu Leu Val Thr Val Ser Ser
130 135

<210> 42
<211> 442
<212> DNA
<213> *Macaca cynomolgus*

<220>
<221> CDS
<222> (1)...(441)

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<400> 42
atg gag ttg gga ctg agc tgg gtt ttc ctt ctt gtt gct att tta aaa      48
Met Glu Leu Gly Leu Ser Trp Val Phe Leu Leu Val Ala Ile Leu Lys
   1           5           10          15

```

```

gg tgc cag tgt gac aag cag ctg gtg cag tcg ggg gga ggc ttg gtc      96
Gly Val Gln Cys Asp Lys Gln Leu Val Gln Ser Gly Gly Gly Leu Val

          20           25           30

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cag cct ggc ggg tct ctg aga ctc gcc tgt gta gcc tcc gga ttc ccc 144
 Gln Pro Gly Gly Ser Leu Arg Leu Ala Cys Val Ala Ser Gly Phe Pro
 35 40 45

ttc agt gac tat tac atg agt tgg gtc cgc cag gct cca ggg aag ggg 192
 Phe Ser Asp Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
 50 55 60

tta gaa tgg ctt gga tta att aaa acc aat cct gat ggt gga acg aca 240

Leu Glu Trp Leu Gly Leu Ile Lys Thr Asn Pro Asp Gly Gly Thr Thr				
65	70	75	80	
				288
gat tac gcc gcg tct gtg aaa ggc aga ttt atc atc tca cga gat gat				
Asp Tyr Ala Ala Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp				
85	90	95		
				336
tca aag aac tca ctg ttc ctt caa atg aac agc ctg aaa acc gag gac				
Ser Lys Asn Ser Leu Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp				
100	105	110		
				384
acg gcc gtg tat tac tgc acc aca gaa gtg ttg gtg gtg tct gct att				
Thr Ala Val Tyr Tyr Cys Thr Thr Glu Val Leu Val Val Ser Ala Ile				
115	120	125		
				432
caa ctc att gga tgt ctg ggg ccc ggg gag ttg tgg tca ccc gtc tct				
Gln Leu Ile Gly Cys Leu Gly Pro Gly Glu Leu Trp Ser Pro Val Ser				
130	135	140		
				442
ttc cgc ttc a				
Phe Arg Phe				
145				
<210> 43				
<211> 407				
<212> DNA				
<213> Macaca cynomolgus				
<220>				
<221> CDS				
<222> (1)...(405)				
<400> 43				
atg aag cac ctg tgg ttc ttc ctc ctg gtg gca gct ccc aga tgg				48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp				
1	5	10	15	

gtc ctg tcc cag gtg cag ttg gag gag tcg ggc cca gga ctg gtg aag	96		
Val Leu Ser Gln Val Gln Leu Glu Ser Gly Pro Gly Leu Val Lys			
20	25	30	
ccc tcg gag acc ctg tcc acc tgc gct gtg tct ggt ggc ctc att	144		
Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Leu Ile			
35	40	45	
act gga aac tac tgg aac tgg ctc cgg cag tca gaa ggg aag gga ctg	192		
Thr Gly Asn Tyr Trp Asn Trp Leu Arg Gln Ser Glu Gly Lys Gly Leu			
50	55	60	
gag tgg att ggc cat att ggt ggt agt agt ggg aac acc ggc tac aac	240		
Glu Trp Ile Gly His Ile Gly Gly Ser Ser Gly Asn Thr Gly Tyr Asn			
65	70	75	80
tcc gct ttc gag agt cgc gtc acc ttg tca aga gac acg gcc aag aat	288		
Ser Ala Phe Glu Ser Arg Val Thr Leu Ser Arg Asp Thr Ala Lys Asn			
85	90	95	
cgg ttc tcc ctg aaa ctg acc tct gtg acc gcc gca gat tcg gcc gtc	336		
Arg Phe Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Ser Ala Val			
100	105	110	
tat tac tgt gcg aga tcg ggt ttt acc ggc acc gac ttc ttt tac tat	384		
Tyr Tyr Cys Ala Arg Ser Gly Phe Thr Gly Thr Asp Phe Phe Tyr Tyr			
115	120	125	
tgg ggc ccg ggg aag tct tgg tc	407		
Trp Gly Pro Gly Lys Ser Trp			
130	135		

<210> 44

<211> 420

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(420)

<400> 44

atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca gct ccc aga tgg	48
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Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
---	--

1

5

10

15

gtc ctg tcc cag gtt caa cta cag gag tcg ggc cca gga ctg atg aag	96
---	----

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Met Lys	
---	--

20

25

30

cct tcg gag acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc	144
---	-----

Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile	
---	--

35

40

45

agc ggt ggt ttt ggc tgg ggc tgg atc cgt cag tcc ccg ggg aag ggg	192
---	-----

Ser Gly Gly Phe Gly Trp Gly Trp Ile Arg Gln Ser Pro Gly Lys Gly	
---	--

50

55

60

ctg gaa tgg att gga agt ttc tat act act act gga aat acc ttc tcc	240
---	-----

Leu Glu Trp Ile Gly Ser Phe Tyr Thr Thr Gly Asn Thr Phe Ser	
---	--

65

70

75

80

aac ccc tcc ctc aag agt cga gtc acc att tca gcg gac acg tcc aag	288
---	-----

Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Ala Asp Thr Ser Lys	
---	--

85

90

95

aac cag ttc tcc ctg aga ctg acc tct gtg acc gcc gcg gac acg gcc	336
---	-----

Asn Gln Phe Ser Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala	
---	--

100

105

110

gtt tat tac tgt gcg aga gat ctc tat agc agc ggc tat aaa ttt tac	384
---	-----

Val Tyr Tyr Cys Ala Arg Asp Leu Tyr Ser Ser Gly Tyr Lys Phe Tyr	
---	--

115

120

125

tac tgg ggc cag gga gtc ctg gtc acc gtc tcc tca
 Tyr Trp Gly Gln Gly Val Leu Val Thr Val Ser Ser

130

135

140

420

<210> 45

<211> 98

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 45

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ala Cys Val Gly Ser Gly Phe Ala Phe Arg Asn Thr
 20 25 30
 Arg Met His Trp Ile Arg Gln Thr Pro Gly Lys Arg Leu Glu Trp Val
 35 40 45
 Ala Asp Ile Lys Phe Asp Gly Ser Asp Phe Tyr Tyr Val Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Glu Met Asn Ser Leu Arg Pro Asp Asp Thr Ala Val Tyr Phe Cys
 85 90 95
 Val Arg

<210> 46
<211> 98
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (31)...(35)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 46

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1															
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Asp	Ser	Ile	Thr	Thr	Val
20															
Phe	Trp	Ser	Trp	Leu	Arg	Gln	Ser	Pro	Gly	Ile	Gly	Leu	Glu	Trp	Ile
35															
Gly	Asn	Phe	Ala	Gly	Ser	Thr	Pro	Glu	Thr	Asn	Tyr	Asn	Pro	Ser	Leu
50															
Lys	Asn	Arg	Ala	Thr	Ile	Ser	Lys	Asp	Thr	Pro	Thr	Asn	Gln	Phe	Phe
65															
Leu	Arg	Leu	Thr	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Phe	Cys
85															
Ala	Arg														

<210> 47
<211> 98
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN

<222> (31) . . . (35)

<223> CDRI

<221> DOMAIN

<222> (50) . . . (66)

<223> CDR II

<400> 47

<210> 48

<211> 98

<212> PRT

<213> *Macaca cynomolgus*

<220>

<221> DOMAIN

<222> (31) . . . (35)

<223> CDRIT

<221> DOMAIN

<222> (50) . . . (66)

5233-2 CDRIT

<400> 48

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Val Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe Ser Thr Tyr
20 25 30

Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Gly Gly Gly Arg Pro Asn Tyr Asn Ser Ser Leu
50 55 60

Lys Ser Arg Ile Thr Leu Ser Leu Asp Ala Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Asn Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg

<210> 49

<211> 98

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 49

Gln Val Gln Leu His Glu Ser Gly Pro Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Asn Val Ser Gly Asp Ser Pro Thr Lys Ser
20 25 30

Thr Trp Asn Trp Val Arg Gln Ser Pro Gly Lys Pro Leu Glu Trp Ile
35 40 45

50

Gly His Val Gly Ser Gly Gly Gly Pro Val Tyr Asn Val Phe Leu
 50 55 60
 Thr Gly Arg Val Ser Met Ser Leu Asp Ala Ser Lys Lys Leu Leu Ser
 65 70 75 80
 Leu Ala Leu Ala Ser Val Thr Ala Ala Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Val Arg

<210> 50
 <211> 100
 <212> PRT
 <213> Macaca cynomolgus

<220>
 <221> DOMAIN
 <222> (31) ... (35)
 <223> CDRI

<221> DOMAIN
 <222> (50) ... (68)
 <223> CDRII

<400> 50
 Asp Lys Gln Leu Val Gln Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ala Cys Val Ala Ser Gly Phe Pro Phe Ser Asp Tyr
 20 25 30
 Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45
 Gly Leu Ile Lys Thr Asn Pro Asp Gly Gly Thr Thr Asp Tyr Ala Ala
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asn Ser
 65 70 75 80
 Leu Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Thr Thr

100

<210> 51
<211> 98
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (31)...(35)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 51

Gln Val Gln Leu Glu Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Leu Ile Thr Gly Asn
20 25 30
Tyr Trp Asn Trp Leu Arg Gln Ser Glu Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly His Ile Gly Gly Ser Ser Gly Asn Thr Gly Tyr Asn Ser Ala Phe
50 55 60
Glu Ser Arg Val Thr Leu Ser Arg Asp Thr Ala Lys Asn Arg Phe Ser
65 70 75 80
Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg

<210> 52
<211> 99
<212> PRT
<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31) . . . (36)

<223> CDRI

<221> DOMAIN

<222> (51) . . . (67)

<223> CDRII

<400> 52

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Met	Lys	Pro	Ser	Glu
1															15
Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Ser	Gly	Gly	Ser	Ile	Ser	Gly	Gly
															30
Phe	Gly	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Lys	Gly	Leu	Glu	Trp
															45
Ile	Gly	Ser	Phe	Tyr	Thr	Thr	Thr	Gly	Asn	Thr	Phe	Ser	Asn	Pro	Ser
															60
Leu	Lys	Ser	Arg	Val	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Gln	Phe
															80
Ser	Leu	Arg	Leu	Thr	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr
															95
Cys	Ala	Arg													

<210> 53

<211> 390

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1) . . . (390)

<400> 53

atg	gac	ata	agg	gtc	ccc	gtg	cag	ctc	ctg	ggg	ctc	ctg	ttg	ctc	tgg
Met	Asp	Ile	Arg	Val	Pro	Val	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp

48

1	5	10	15	
				96
ctc cga ggt gcc aga tgt gac atc cag atg acc cag tct cca tcc tcc Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser				
20	25	30		
				144
ctg tct aca tct gta gga gac act gtc acc atc act tgc cgg gcg agt Leu Ser Thr Ser Val Gly Asp Thr Val Thr Ile Thr Cys Arg Ala Ser				
35	40	45		
				192
caa ggc att gac acg gag tta gcc tgg tat cag cag aaa cca ggt aaa Gln Gly Ile Asp Thr Glu Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys				
50	55	60		
				240
gcc ccc aca ctc ctg atc tct gat gcc tcc agg ttg cag acg ggg gtc Ala Pro Thr Leu Leu Ile Ser Asp Ala Ser Arg Leu Gln Thr Gly Val				
65	70	75	80	
				288
tca tct cgg ttc agc ggc agt gga tct gga aca gat ttc act ctc acc Ser Ser Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr				
85	90	95		
				336
atc aac agc ctg cag cct gaa gat att gcg act tat tac tgt caa cag Ile Asn Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln				
100	105	110		
				384
gat aat agt ttt cca ctc act ttc ggc gga ggg acc aag gtg gag atc Asp Asn Ser Phe Pro Leu Thr Phe Gly Gly Thr Lys Val Glu Ile				
115	120	125		
				390
aaa cga				
Lys Arg				
130				

<210> 54

<211> 384

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(384)

<400> 54

gtc ttc att tcc ctg ttg ctc tgg atc tct ggt gcc tgt ggg gac att 48

Val Phe Ile Ser Leu Leu Leu Trp Ile Ser Gly Ala Cys Gly Asp Ile

1 5 10 15

gtg atg acc cag tct cca gac tcc ctg gct gtg tct ctg gga gag agg 96

Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg

20 25 30

gtc acc atc aat tgt aag tcc agc cag agt ctt tta tac agc tcc aac 144

Val Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Ser Asn

35 40 45

aat aag aac tac tta gcc tgg tac cag caa aaa cca gga cag gct cct 192

Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro

50 55 60

caa cta ctc att tac tgg gca tct acc cgg gaa tcc ggg gtc cct aat 240

Gln Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asn

65 70 75 80

cga ttt agt ggc agc ggc tct ggg aca gat ttc act ctc acc atc agt 288

Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser

85 90 95

ggc ctg cag gct gaa gat gtg gca gtg tat tac tgt caa cag tat tat 336

Gly Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr

100 105 110

gat atg ccc gac agt ttt ggc cag ggg acc aaa gtg gac atc aaa cga 384

Asp Met Pro Asp Ser Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg
 115 120 125

<210> 55

<211> 399

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(399)

<400> 55

atg agg ctc cct gct cag ctc ctg ggg ctg cta ttg ctc tgc gtc ccc 48
 Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Leu Cys Val Pro
 1 5 10 15

gga tcc agt ggg gat gtt gtg atg act cag tct cca ctc tcc ctg ccc 96
 Gly Ser Ser Gly Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro
 20 25 30

gtc atc cct gga cag cca gcc tcc atc tcc tgc agg tct agt caa agc 144
 Val Ile Pro Gly Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
 35 40 45

ctt gta cat agt gac ggg aaa acc tac ttg aat tgg tta caa cag aag 192
 Leu Val His Ser Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys
 50 55 60

cca ggc caa cct cca aga ctc ctg att tat cag gtt tct aac cgg cac 240
 Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Gln Val Ser Asn Arg His
 65 70 75 80

tct ggg gtc cca gac aga ttc agc ggc agt ggg gca ggg aca gac ttc 288
 Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe
 85 90 95
 56

aca ctg aaa atc agc aga gtg gag act gag gat gtt ggg gtt tat tcc	336
Thr Leu Lys Ile Ser Arg Val Glu Thr Glu Asp Val Gly Val Tyr Ser	
100	105
	110
 tgc gtg caa ggt aca cac tgg ccg tgg acg ttc ggc caa ggg acc aag	384
Cys Val Gln Gly Thr His Trp Pro Trp Thr Phe Gly Gln Gly Thr Lys	
115	120
	125
 gtg gac atc aaa cga	399
Val Asp Ile Lys Arg	
130	
 <210> 56	
<211> 384	
<212> DNA	
<213> Macaca cynomolgus	
 <220>	
<221> CDS	
<222> (1)...(384)	
 <400> 56	
atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg ctc cca	48
Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Pro	
1	5
	10
	15
 gg t gc ata tgt gac att cag atg tcc cag tct cca tcc tcc ctg tct	96
Gly Ala Ile Cys Asp Ile Gln Met Ser Gln Ser Pro Ser Ser Leu Ser	
20	25
	30
 gct tct gtg gga gac aga gtc acc atc acc tgc cgg gca agt cag ggc	144
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly	
35	40
	45
 ata act aat tat tta aac tgg tat cag cag aaa ccg ggg aaa gcc cct	192
	57

Ile Thr Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro			
50	55	60	
aac ctc ctg atc tat tat gca act cgt ttg gcg agc ggg gtc cca tca			240
Asn Leu Leu Ile Tyr Tyr Ala Thr Arg Leu Ala Ser Gly Val Pro Ser			
65	70	75	80
agg ttc agc ggc agt gga tct ggg tcg gag tac agt ctc gcc atc agc			288
Arg Phe Ser Gly Ser Gly Ser Glu Tyr Ser Leu Ala Ile Ser			
85	90	95	
agc ctg cag cct gaa gat ttt gca acc tat ttc tgt caa cag ggt tat			336
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Tyr			
100	105	110	
agg gcc ccc tac act ttt ggc cag ggg acc aca gtg gag atc aaa cga			384
Arg Ala Pro Tyr Thr Phe Gly Gln Gly Thr Thr Val Glu Ile Lys Arg			
115	120	125	
<210> 57			
<211> 390			
<212> DNA			
<213> Macaca cynomolgus			
<220>			
<221> CDS			
<222> (1)...(390)			
<400> 57			
atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg			48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp			
1	5	10	15
ctc cta ggt gcc aga tgt gac atc cag atg acc cag tct cct tct tcc			96
Leu Leu Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser			
20	25	30	
58			

ttg tct gca tct gta gga gac aga gtc acc atc act tgc caa gcc agt	144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser	
35	40
	45
cag ggt att agc aac tgg tta gcc tgg tat cag cag aaa ccg ggg aaa	192
Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys	
50	55
	60
gcc cct aag ctc ctg atc tat gct gca tcc act ttc caa agt ggg gtc	240
Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Thr Phe Gln Ser Gly Val	
65	70
	75
	80
cca tca agg ttc agc ggc agt gga tct ggg aca gag ttc act ctc acc	288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr	
85	90
	95
atc agc agc ctg cag cct gaa gat ttt gca act tac tac tgt caa cag	336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln	
100	105
	110
tat aat act tac cct ctc act ttc ggc gga ggg acc aag gtg gag atc	384
Tyr Asn Thr Tyr Pro Leu Thr Phe Gly Gly Thr Lys Val Glu Ile	
115	120
	125
aaa cga	390
Lys Arg	
130	

<210> 58
<211> 390
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS

<222> (1)...(390)

<400> 58

atg gac ttg agg gcc ccc gct cat ctc cta ggg ctc ctg ctg ctc tgg	48	
Met Asp Leu Arg Ala Pro Ala His Leu Leu Gly Leu Leu Leu Trp		
1 5 10 15		
ctc cca ggt gcc aga ggt gac atc cag atg acc cag tct cca ccc tcc	96	
Leu Pro Gly Ala Arg Gly Asp Ile Gln Met Thr Gln Ser Pro Pro Ser		
20 25 30		
ctg tct gcg tct gtt ggg gac act gtc agt ctt act tgt cgg gca agt	144	
Leu Ser Ala Ser Val Gly Asp Thr Val Ser Leu Thr Cys Arg Ala Ser		
35 40 45		
cag cct att ggc agt aat tta aat tgg ttc cag caa aaa cct ggg agc	192	
Gln Pro Ile Gly Ser Asn Leu Asn Trp Phe Gln Gln Lys Pro Gly Ser		
50 55 60		
ccc ccc aga ctc ctg atc tac ctt gcg acc gcc ttg caa cgt ggg atc	240	
Pro Pro Arg Leu Leu Ile Tyr Leu Ala Thr Ala Leu Gln Arg Gly Ile		
65 70 75 80		
ccg tca agg ttt agc gcc act gga tct caa acc aat ttc act ctc acg	288	
Pro Ser Arg Phe Ser Ala Thr Gly Ser Gln Thr Asn Phe Thr Leu Thr		
85 90 95		
atc acc ggc ctg cag cct gag gat ttc gca act tac ctc tgt ctg caa	336	
Ile Thr Gly Leu Gln Pro Glu Asp Phe Ala Thr Tyr Leu Cys Leu Gln		
100 105 110		
cat act tct tac cca ttc act ttt ggc ccc ggg aca aag gtg gat atc	384	
His Thr Ser Tyr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile		
115 120 125		
aag cga	390	
Lys Arg		

130

<210> 59
<211> 88
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(56)
<223> CDRII

<400> 59

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Thr	Ser	Val	Gly
1							5					10			15
Asp	Thr	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Asp	Thr	Glu
				20								25			30
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Thr	Leu	Leu	Ile
				35								40			45
Ser	Asp	Ala	Ser	Arg	Leu	Gln	Thr	Gly	Val	Ser	Ser	Arg	Phe	Ser	Gly
				50								55			60
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asn	Ser	Leu	Gln	Pro
				65								70			75
Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys								80
							85								

<210> 60
<211> 94
<212> PRT
<213> Macaca cynomolgus

<220>

<221> DOMAIN
<222> (24)...(40)
<223> CDRI

<221> DOMAIN
<222> (56)...(62)
<223> CDRII

<400> 60

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
1															15
Glu	Arg	Val	Thr	Ile	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Leu	Leu	Tyr	Ser
				20					25					30	
Ser	Asn	Asn	Lys	Asn	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln
					35				40					45	
Ala	Pro	Gln	Leu	Leu	Ile	Tyr	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Val
					50				55					60	
Pro	Asn	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr
					65				70					75	
Ile	Ser	Gly	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys		
									85					90	

<210> 61
<211> 93
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (24)...(39)
<223> CDRI

<221> DOMAIN
<222> (54)...(61)
<223> CDRII

<400> 61

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ile Pro Gly				
1	5	10	15	
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser				
20	25	30		
Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Gln Pro				
35	40	45		
Pro Arg Leu Leu Ile Tyr Gln Val Ser Asn Arg His Ser Gly Val Pro				
50	55	60		
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile				
65	70	75	80	
Ser Arg Val Glu Thr Glu Asp Val Gly Val Tyr Ser Cys				
85	90			

<210> 62

<211> 88

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN

<222> (50)...(56)

<223> CDRII

<400> 62

Asp Ile Gln Met Ser Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly				
1	5	10	15	
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Thr Asn Tyr				
20	25	30		
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Ile				
35	40	45		
Tyr Tyr Ala Thr Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly				
50	55	60		
Ser Gly Ser Gly Ser Glu Tyr Ser Leu Ala Ile Ser Ser Leu Gln Pro				

65

70

75

80

Glu Asp Phe Ala Thr Tyr Phe Cys

85

<210> 63

<211> 88

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (24) . . . (34)

<223> CDRI

<221> DOMAIN

<222> (50) . . . (56)

<223> CDRII

<400> 63

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1

5

10

15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Gly Ile Ser Asn Trp

20

25

30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35

40

45

Tyr Ala Ala Ser Thr Phe Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50

55

60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65

70

75

80

Glu Asp Phe Ala Thr Tyr Tyr Cys

85

<210> 64

<211> 88

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (24) . . . (34)

<223> CDRI

<221> DOMAIN

<222> (50) . . . (56)

<223> CDRII

<400> 64

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Pro	Ser	Leu	Ser	Ala	Ser	Val	Gly
1															
Asp	Thr	Val	Ser	Leu	Thr	Cys	Arg	Ala	Ser	Gln	Pro	Ile	Gly	Ser	Asn
20															
Leu	Asn	Trp	Phe	Gln	Lys	Pro	Gly	Ser	Pro	Pro	Arg	Leu	Leu	Ile	
35															
Tyr	Leu	Ala	Thr	Ala	Leu	Gln	Arg	Gly	Ile	Pro	Ser	Arg	Phe	Ser	Ala
50															
Thr	Gly	Ser	Gln	Thr	Asn	Phe	Thr	Leu	Thr	Ile	Thr	Gly	Leu	Gln	Pro
65															
Glu	Asp	Phe	Ala	Thr	Tyr	Leu	Cys								

85

<210> 65

<211> 360

<212> DNA

<213> Rat

<220>

<221> CDS

<222> (1) . . . (360)

<400> 65

gac	acg	gtg	ctg	acc	cag	tct	cct	gct	ttg	gct	gtg	cct	cca	gga	gag
															48
Asp	Thr	Val	Leu	Thr	Gln	Ser	Pro	Ala	Leu	Ala	Val	Pro	Pro	Gly	Glu
1															

65

agg gtt acc gtc tcc tgt agg gcc agt gaa agt gtc agt aca ttt ttg			96
Arg Val Thr Val Ser Cys Arg Ala Ser Glu Ser Val Ser Thr Phe Leu			
20	25	30	
cac tgg tat caa cag aaa cca gga cat caa ccc aaa ctc ctc atc tat			144
His Trp Tyr Gln Gln Lys Pro Gly His Gln Pro Lys Leu Leu Ile Tyr			
35	40	45	
cta gcc tca aaa cta gaa tct ggg gtc cct gcc agg ttc agt ggc ggt			192
Leu Ala Ser Lys Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Gly			
50	55	60	
ggg tct ggg aca gac ttc acc ctc acc att gat cct gtg gag gct gat			240
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Pro Val Glu Ala Asp			
65	70	75	80
gac act gct acc tat tac tgt cag cag acc tgg aat gat cct cgg acg			288
Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Thr Trp Asn Asp Pro Arg Thr			
85	90	95	
ttc ggt gga ggc acc aag ctg gaa ttg aaa cgg gct gat gct gca cca			336
Phe Gly Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro			
100	105	110	
act gta tct atc ttc cca cca tcc			360
Thr Val Ser Ile Phe Pro Pro Ser			
115	120		

<210> 66

<211> 360

<212> DNA

<213> Rat

<220>

<221> CDS

<222> (1)...(360)

<400> 66

gag	gtc	cag	ctg	cag	cag	tct	gga	cct	gag	gtt	ggg	agg	cct	ggg	tcc	48
Glu	Val	Gln	Leu	Gln	Ser	Gly	Pro	Glu	Val	Gly	Arg	Pro	Gly	Ser		
1									10						15	

tca	gtc	aag	att	tct	tgc	aag	gct	tct	ggc	tac	acc	ttt	aca	gat	tac	96
Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Tyr	
										20			25		30	

gtt	ttg	aat	tgg	gtg	aag	cag	agt	cct	gga	cag	gga	ctg	gaa	tgg	ata	144
Val	Leu	Asn	Trp	Val	Lys	Gln	Ser	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile	
										35			40		45	

gga	tgg	att	gat	cct	gac	tat	ggt	act	act	gat	tat	gct	gag	aag	ttc	192
Gly	Trp	Ile	Asp	Pro	Asp	Tyr	Gly	Thr	Thr	Asp	Tyr	Ala	Glu	Lys	Phe	
										50			55		60	

aaa	aag	aag	gcc	aca	ctg	act	gca	gat	aca	tcc	tcc	agc	aca	gcc	tac	240
Lys	Lys	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Ser	Ser	Thr	Ala	Tyr	
										65			70		75	80

atc	cag	ctt	agc	agc	ctg	aca	tct	gag	gac	aca	gcc	acc	tat	ttt	tgt	288
Ile	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	
										85			90		95	

gct	aga	tct	agg	aat	tac	gga	gga	tat	att	aat	tac	tgg	ggc	caa	gga	336
Ala	Arg	Ser	Arg	Asn	Tyr	Gly	Gly	Tyr	Ile	Asn	Tyr	Trp	Gly	Gln	Gly	
										100			105		110	

gtc	atg	gtc	aca	gtc	tcc	tca	gct									360
Val	Met	Val	Thr	Val	Ser	Ser	Ala									
										115			120			

<210> 67

<211> 109

<212> PRT

<213> Pan troglodytes

<400> 67

Ala Val His Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Ser Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Ile Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Phe Asp Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Arg Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Gly Trp Gly Thr His Pro
85 90 95
Tyr Asn Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 68

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> rat/chimpanzee sequence

<400> 68

Asp Thr Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Ser Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Ser Thr Phe
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Leu Ala Ser Lys Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Arg Ser Leu Gln Pro

65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Trp Asn Asp Pro Arg			
85	90	95	
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg			
100	105		

<210> 69
<211> 128
<212> PRT
<213> Pan troglodytes

<400> 69

Glu Val Gln Leu Val Glu Ser Gly Gly Val Val Gln Pro Gly Gly			
1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Phe			
20	25	30	
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile			
35	40	45	
Ser Leu Val Ser Trp Asp Ser Tyr Asn Ile Tyr His Ala Asp Ser Val			
50	55	60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Ser Leu Tyr			
65	70	75	80
Leu Gln Met Asn Asp Leu Arg Pro Glu Asp Thr Ala Ile Tyr Phe Cys			
85	90	95	
Ala Lys Ala Asp Thr Gly Asp Phe Asp Tyr Val Ser Asp Ser Trp			
100	105	110	
Arg Cys Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser			
115	120	125	

<210> 70
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> rat/chimpanzee sequence

<400> 70

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Val Leu Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45

Gly Trp Ile Asp Pro Asp Tyr Gly Thr Thr Asp Tyr Ala Glu Lys Phe
 50 55 60

Lys Lys Ala Thr Leu Ser Ala Asp Thr Ser Arg Asn Ser Ala Tyr
 65 70 75 80

Leu Gln Met Asn Asp Leu Arg Pro Glu Asp Thr Ala Ile Tyr Phe Cys
 85 90 95

Ala Arg Ser Arg Asn Tyr Gly Gly Tyr Ile Asn Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser
 115

<210> 71

<211> 354

<212> DNA

<213> Murine

<220>

<221> CDS

<222> (1)...(354)

<400> 71

caa gtt cag ctt caa cag tct gga gct gag ctg atg aag cct ggg gcc 48
 Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
 1 5 10 15

tca gtg aag ata tcc tgc aag gct act ggc tac aca ttc agt agc tac 96
 Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr
 20 25 30

tgg ata gag tgg gta aag cag agg cct gga cat ggc ctt gag tgg att 144

Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile				
35	40	45		
 gga gag att tta cct aga agt ggt aat act aac tac aat gag aag ttc				192
Gly Glu Ile Leu Pro Arg Ser Gly Asn Thr Asn Tyr Asn Glu Lys Phe				
50	55	60		
 aag ggc aag gcc aca ttc act gca gaa aca tcc tcc aac aca gcc tac				240
Lys Gly Lys Ala Thr Phe Thr Ala Glu Thr Ser Ser Asn Thr Ala Tyr				
65	70	75	80	
 atg caa ctc agc agc ctg aca cct gag gac tct gcc gtc tat tac tgt				288
Met Gln Leu Ser Ser Leu Thr Pro Glu Asp Ser Ala Val Tyr Tyr Cys				
85	90	95		
 tca agt cgc ggc gtc agg ggc tct atg gac tac tgg ggt caa gga acc				336
Ser Ser Arg Gly Val Arg Gly Ser Met Asp Tyr Trp Gly Gln Gly Thr				
100	105	110		
 tca gtc acc gtc tcc tca				354
Ser Val Thr Val Ser Ser				
115				
 <210> 72				
<211> 324				
<212> DNA				
<213> Murine				
 <220>				
<221> CDS				
<222> (1)...(324)				
 <400> 72				
gat att cag atg acc cag act aca tcc tcc ctg tct gcc tct ctg gga				48
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly				
1	5	10	15	

gac aga gtc acc atc act tgc agg tca agt cag gac att agc aat ttt			96
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Asp Ile Ser Asn Phe			
20	25	30	
tta aac tgg tat cag cag aaa cca gat gga act gtt aaa ctc ctg atc			144
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile			
35	40	45	
tac tac aca tca aca tta cac tca gga gtc cca tca agg ttc agt ggc			192
Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly			
50	55	60	
agt ggg tct gga aca gat tat tct ctc acc att agc aac ctg gag caa			240
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln			
65	70	75	80
gaa gat att gcc act tac ttt tgc caa cag ggt aat acg ctt cct tgg			288
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp			
85	90	95	
acg ttc ggt gga ggc acc aac ctg gaa atc aaa cgg			324
Thr Phe Gly Gly Thr Asn Leu Glu Ile Lys Arg			
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 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
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 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Trp
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 20 25 30
 Trp Ile Glu Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Leu Pro Arg Ser Gly Asn Thr Asn Tyr Asn Glu Lys Phe
 50 55 60
 Lys Gly Lys Ala Ser Phe Asn Ala Asp Thr Ser Thr Asn Ile Ala Tyr
 65 70 75 80
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 Leu Val Thr Val Ser Ser

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48

tca gtg aag ctg tcc tgc aag gct tct ggc agt acc ttc acc agc tac
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Ser Thr Phe Thr Ser Tyr
20 25 30

96

tgg atg cac tgg gtg aag cag agg cct gga cga ggc ctt gag tgg att
Trp Met His Trp Val Lys Gln Arg Pro Gly Arg Gly Leu Glu Trp Ile
35 40 45

144

gga agg att gat cca aat agt ggt act aag gat aat gag aag ttc
Gly Arg Ile Asp Pro Asn Ser Gly Thr Lys Asp Asn Glu Lys Phe
50 55 60

192

aag agc aag gcc aca ctg act gta gac aaa ccc tcc agc aca gcc tac
Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Pro Ser Ser Thr Ala Tyr
65 70 75 80

240

atg cag ctc agc agc ctg aca tct gag gac tct gcg gtc tat tat tgt
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

288

gca aga gag acc tac tat gat tcc tcg ttt gct tac tgg ggc caa ggg

336

Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly
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gac agg gtc agc gtc acc tgc aag gcc agt cag aat gtg ggt act aat      96
Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn

          20           25           30

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5560

gaa gac ttg gca gag tat ttc tgt cag caa tat aac agc tat cct ctc 288
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 35 40 45
 Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
 85 90 95
 Thr Phe Gly Gly Lys Val Glu Ile Lys
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<210> 78
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20 25 30
Trp Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Asp Asn Glu Lys Phe
50 55 60
Lys Ser Lys Ala Thr Leu Asn Val Asp Lys Ser Thr Asn Ile Ala Tyr
65 70 75 80
Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly
100 105 110
Thr Met Val Thr Val Ser
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Thr Phe Thr Ser Tyr
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Trp Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

35	40	45
Gly Arg Ile Asp Pro Asn Ser Gly	Gly Thr Lys Asp Asn Glu Lys Phe	
50	55	60
Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr		
65	70	75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys		80
85	90	95
Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly		
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Thr Met Val Thr Val Ser Ala		
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20	25	30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile		
35	40	45
Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
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<210> 85
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<210> 87
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<400> 87
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
1 5 10

<210> 88
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1 5 10

<210> 96

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Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
1 5 10

<210> 97

<211> 11

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<213> Pan troglodytes

<400> 97

Phe Gly Gly Thr Lys Val Glu Ile Lys Arg
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INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/09131

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 39/395
 US CL : 530/387.3; 424/133.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.3; 424/133.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Medline, Biosis
 search terms: immunoglobulin, antibody, framework regions, CDR grafted, humanized, primatized

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANDERSON et al. A primatized MAb to Human CD4 causes receptor modulation without marked reduction in CD4+ T cells in Chimpanzees: In vitro and in vivo characterization of a MAb (IDECE9.1) to human CD4. Clinical Immunology and Immunopathology. July 1997, Vol. 84, No. 1, pages 73-84, see entire document.	1-19

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* "A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* "E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A"	document member of the same patent family
* "O" document referring to an oral disclosure, use, exhibition or other means		
* "P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

26 JULY 1999

Date of mailing of the international search report

18 AUG 1999

Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Faxsimile No. (703) 305-3230

Authorized officer

JULIE BURKE

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/09131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 20-31 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
the claim contain specific sequence identification numbers however the application has not complied with the sequence requirements.

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.